THE TRACHEA
and
CUFF-INDUCED TRACHEAL INJURY

An experimental study on causative factors and prevention

By

ULF NORDIN

UPPSALA 1977

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II. Nordin, U., Engström, B. & Lindholm, C-E. 1977. Surface structure of the tracheal wall after different durations of intubation. *Acta Otolaryngol* (Stockh) *Suppl 345.*

III. Nordin, U. & Lindholm, C-E. 1977. The Vessels of the Rabbit Trachea and Ischemia Caused by Cuff Pressure. *Arch Oto-Rhino-Laryngol. 215, 11.*

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ABSTRACT

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Prolonged tracheal intubation with a cuffed tube can cause clinically significant tracheal stenosis.

It is well known that the *small (high-pressure) cuff* often causes deep ulceration of the mucosa covering the tracheal cartilages. It can be predicted that this type of cuff will stop the microcirculation in the mucosa on top of the cartilages at a cuff-to-tracheal wall pressure (C-T pressure) exceeding 30 mmHg. The small cuff, however, cannot seal at such a low C–T pressure.

The *large (low-pressure) cuff*, which is evaluated in this dissertation, is, properly handled, more benign to the trachea.

The large cuff will seal at a low C–T pressure. Any intubation, however, causes some superficial damage to the tracheal mucosa, the depth being directly related to C–T pressure. This pressure has greater importance for the degree of damage than has the duration of intubation. Thus, if the C–T pressure is kept low, the trachea will resist even prolonged cuffed intubation.

The large cuff must have a *resting diameter* well above that of the trachea. This means that the cuff will allow high intracuff pressures to be transmitted undiminished to the tracheal wall until the tracheal diameter exceeds the cuff diameter, when *circumferential tension within the cuff* will start to limit the effective C–T pressure. The trachea is then already dilated, and the physics of seal is changed from that of the large cuff to that of the small (high-pressure) cuff.

The *quality of the cuff wall* is very important. If the large cuff has thick, stiff walls, it tends to cause lesions similar to those caused by a small cuff.

Irritation of the tracheal mucosa, e.g. caused by intubation, increased the blood flow in the mucosa from 0.62 ± 0.41 ml/min·g to 3.22 ± 1.55 ml/min·g. In the irritated mucosa the hydrostatic pressure was 28 mmHg in the early part of the capillaries, 17 mmHg in the middle part and 14 mmHg in the late part. The pressure in the veins was 12 mmHg and in the interstitium 3–4 mmHg. The irritation also caused heavy leakage of protein from the vascular bed into the interstitium, where the colloid osmotic pressure increased. All this led to filtration of fluid from all the vascular structures identified into the interstitium, causing mucosal edema. The risk of edema was diminished, however, with the body upright. The fluid flowing into the interstitium was drained by two routes. A protein-free fraction was reabsorbed by the secretory glands for production of mucus. The increased mucus production will assist the trachea in its attempt to remove the foreign body which has originally caused this reaction. A protein-rich part of the fluid was drained by the lymphatic system.

The *ideal large cuff* should have as thin and pliable walls as possible, so as to completely drape the inside of the trachea and exert almost the same pressure over the entire mucosa. Under such circumstances mucosal blood flow will be decreased when C–T pressure exceeds 30 mmHg, but nutritive blood flow will not completely stop until C–T pressures far exceeding 30 mmHg are reached. Thus the tracheal vascular supply seems to have an inbuilt mechanism which tends to preserve a certain blood perfusion, even in the musoca covering the cartilages, when pressure is exerted by an *ideal* large cuff, at least for short periods. Although C–T pressures far exceeding 30 mmHg may be regarded as not catastrophic for a limited time, they should absolutely not be abused.

It is strongly recommended that a thin-walled large cuff is used without exception, and that the cuff pressure is monitored and kept below 20 mmHg.

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Introduction

Tracheal intubation has a long and interesting history and is still an indispensable part of modern medical care.

When Trendelenburg (1871) described the first tracheostomy cannula supplied with an inflatable cuff he introduced a method of producing a seal between the cannula and the tracheal wall which, in principle, is still used today. Trendelenburg's cuff was small and thick-walled, a typical representative of the so called *low-volume cuff**. Some years later Eisenmenger (1893) introduced the first *high-volume cuff* and brought an improvement not only in respect to the cuff size. In addition, he supplied the cuff with a large pilot balloon which was to signal and possibly also limit the intracuff pressure. Eisenmenger was probably not fully aware of the true significance of the cuff volume—at least he published no analysis of the practical difference between a high-volume and a low-volume cuff. Wilms (1904) described a tube supplied with a high-volume cuff, in which holes had been made in the tube wall within the cuff area, so that the pressure in the airway should automatically inflate the cuff. The system was unsatisfactory, however, as the holes easily became blocked with mucus. This device was reintroduced by Mushin (1943).

The first analysis of the practical difference between the low- and high-volume cuff was reported by Grimm & Knight (1943). They recommended the use of a high-volume cuff with a sufficiently large volume to allow it to fill the lumen of the trachea without the cuff wall being stretched. Concerning the low-volume cuff, they state:

"The heavy walls require considerable air pressure to expand these small cuffs to a volume sufficient to fill the trachea. Since tracheae vary in size, it follows that an unknown amount of pressure is required to fill the trachea without applying any pressure to the mucosa. Therefore, in such a cuff, it is impossible to measure the pressure applied to the tracheal mucosa. This is of paramount importance since an undue amount of pressure causes either trauma or ischemia which causes a slough of the mucosa."

In 1947 Sanders constructed a high-volume slip-on cuff for use on a silver tracheostomy cannula, and Safar et al. (1962) noted that this cuff could be used for up to four months during artificial ventilation without any major complications, but they were unaware of the reasons for these good results.

The recommendation of Grimm & Knight was otherwise not heeded widely, and the majority of cuffs used throughout the world were of the low-volume type. The really great breakthrough for the use of cuffed tubes, however, came during the polio epidemics in Europe in the beginning of the 1950s and in the U.S.A. in the early 1960s, in artificial respiration in patients with respiratory insufficiency. At about the same time intensive care began its rapid development and prolonged mechanical ventilation of severely injured patients became increasingly common. Previously the lives of such patients often could not be saved, so that

* Technical terms used in this thesis are explained in the chapters "Definitions" and "Cuff characteristics" (p. 11, 13).

complications of the artificial ventilation in itself never came to light. Now, when an increasing number of patients could be cured, the wider use of low-volume cuffs gave rise to a considerable increase in reports of ulceration on the tracheal wall, tracheomalacias with consequent stenosis, and sometimes tracheo-esophageal fistulas. This began to comprise a great problem all over the world, from the beginning of the 1960s onwards. Clinically significant tracheal stenoses were reported in frequencies of up to 20 % (Grillo 1970).

In view of the constantly increasing frequency of complications, during the second half of the 1960s analyses of the cause of the tracheal injuries were initiated in several centers.

Some of the more important investigations concerning tracheal damage caused by tracheal cuffs were undertaken in Scandinavia by Lomholt (1967) and Lindholm (1969).

In the U.S.A. and Canada this problem was studied by research groups in Pittsburgh (Carroll et al. 1969, Hedden et al. 1969), Boston (Cooper & Grillo 1969, Geffin & Pontoppidan 1969) and Toronto (Bryce et al. 1968).

The general conclusion from these investigations was that the small-resting-diameter, small-residual-volume cuff (hereinafter called the *small cuff*) has to be inflated with a pressure of sometimes up to 200 mmHg just to reach the tracheal wall (Carroll et al. 1969). Owing to its low residual volume, the cuff is stretched—to varying degrees—when the tracheal wall is reached. In this way the cuff wall itself will take up an unknown proportion of the pressure in the cuff, which means that an idea of the cuff-to-tracheal wall pressure (C-T pressure) cannot be obtained by measuring the intracuff pressure. In clinical practice uncontrollable and often very high C-T pressures were considered to be the fundamental cause of the tracheal injuries following prolonged tracheal intubation. Yet another cause of the frequent occurrence of high C-T pressures with the use of small cuffs was found. For every superfluous milliliter of air that was insufflated into the cuff "for safety's sake", a steep rise of the C-T pressure was noted (see "slope pressure" under "Definitions" and "Cuff characteristics", p. 11, 13).

These experiences led to the recommendation by several authors (Lomholt 1967, Carroll et al. 1969, Cooper & Grillo 1969) that the small cuff be replaced by the large-resting-diameter, large-residual-volume cuff, in the following called the *large cuff*.

Lomholt (1967) states: "The only simple way to control the lateral pressure of the cuff is to produce a cuff having an inside pressure exactly equal to the pressure on the tracheal wall. These requirements are fulfilled if the cuff is made of a thin inelastic plast-film and so large that it will never be fully expanded, but will lie in folds against the tracheal wall". Lomholt proposed a cuff diameter of 35 mm.

On the basis of simultaneous measurements of the intracuff pressure, airway pressure and C-T pressure in anesthetized dogs, Carroll et al. (1969) claimed that with *any* large cuff the intracuff and C-T pressures are identical (as long as there is no circumferential tension in the cuff wall), that there is a low slope pressure at inflation beyond "sealing", and that sealing is achieved at low C-T pressures; all compared with small cuffs. They also found that the intracuff pressure automatically cycles in synchrony with the airway pressure without use of any gadgets so long as the cuff is of adequately large diameter and large volume.

This means that the resting C-T pressure with large cuffs can be much lower than the peak airway pressure and yet provide a seal. Thus the *mean pressure* against the tracheal mucosa can be much lower than the peak tracheal pressure. That is, if the patient is being ventilated at a pressure of 30 centimeters of water, and if an intracuff pressure of 15 centimeters of water is found adequate to prevent aspiration, then the patient's tracheal mucosa will be exposed to a pressure of 15 centimeters of water during the two-thirds of the time that he is in passive exhalation up to a pressure of 30 centimeters of water at the end of the one-third of the time that he is undergoing positive pressure lung inflation.

To compensate for the scarcity of acceptable commercially available large cuffs, Geffin & Pontoppidan (1969) "prestretched" small plastic cuffs and converted them into large ones. Those who

followed this recommendation noted a clear decrease of acute tracheal injuries after intubation (Grillo et al. 1971).

Large cuffs of good quality became available, however, during the first half of the 1970s, and the use of this type of cuff has since increased. Tracheal surgeons all over the world have noticed a considerable reduction of the frequency of clinically significant cuff-induced tracheal stenosis.

In recent years several convincing investigations have demonstrated a reduction of cuff-induced tracheal injuries with the use of large cuffs, as compared with the small type (Grillo et al. 1971, Ching et al. 1971, Dunn et al. 1974, Mathias & Wedley 1974, Paegle & Bernhard 1975).

In the present investigation interest was therefore focused on the *large cuff* and no comparative studies were made between the large and small types. The hitherto most extensive investigation of the physical properties and functional aspects of the large cuff is that published by Carroll et al. (1974).

Several different types of *safety devices* have been tried over the years with the aim of diminishing tracheal damage by the cuff.

The pilot balloon used by Eisenmenger (1893) and the holed tube described by Wilms (1904) and Mushin (1943) have been mentioned above.

Lauria & Andersen (1969) connected the cuff inflation tube to a side arm at the ventilator connection to the tracheal tube. This prevented the connecting holes from being plugged with secretion. Neither this nor Wilm's system, however, gave full protection against aspiration in the expiratory phase.

Lomholt (1971) desribed a system in which the cuff is inflated from a separate low-pressure gas source during expiration. This equipment is not yet commercially available.

Kamen & Wilkinson (1971) suggested a different solution to the problem. Their device consists of a large polyurethane foam-filled cuff from which the air is aspirated at intubation. The insufflation channel is then left open, whereupon the foam-cuff expands by its own force, which, however, is adjusted so that a high C-T pressure cannot occur *if the relation between the cuff and tracheal diameters is optimal.* This cuff seems to function well, although a problem may arise in that the foam may change shape with time, possibly related to the absorption of moisture, allowing audible air leak to occur at 18 to 36 hours of intubation. The cuff is available on the market but is expensive.

McGinnis et al. (1971) has connected the cuff to a pressure limiting balloon which maximates the intracuff pressure to 18 mmHg even when the cuff is inflated with up to 36 ml more air than is required for no-leak ventilation. The system is commercially available and seems to work well. However, if the patient happens to lie on the balloon, or if this is compressed inadvertently by the personnel, the intracuff pressure will rise.

Specific background of this study

Several decades ago, in 1943, Grimm & Knight pointed out the risk of *local ischemia* of the tracheal mucosa due to excessively high pressure from the cuff wall. In a large number of subsequent investigations in this field it has been assumed that local ischemia is a very important cause of tracheal injuries following endotracheal intubation. In practically every study on this subject speculations have been made on the level of C-T pressure at which the ischemia might occur. To analyse this matter further, it was considered of interest to ascertain the perfusion pressure in the rabbit tracheal mucosal capillaries, in order to obtain an idea about when the pressure of a tracheal tube cuff on the mucosa can be expected to stop the capillary blood flow, i.e. to cause local ischemia, with a consequent risk of tracheal damage and stenosis.

The aim of the present investigation was to elucidate the effect of intubation with a cuffed tracheal tube on the rabbit tracheal wall. Interest was focused on the importance of the shape, construction and handling of the inflatable cuff.

An attempt was made to answer the following specific questions:

1. What can be done to minimize tracheal damage at intubation?
2. Does a safe C-T pressure exist?
3. If so, what pressure range may be generally regarded as safe?

The problems were approached with respect to

1. Ultrastructural aspects (Papers I and II); phase contrast microscopy and transmission and scanning electron microscopy were used to study the mucosal surface damage caused by the cuff.
2. The vascular anatomy of the tracheal wall (Paper III); here the normal anatomy was studied and compression of the mucosal vascular bed by an inflated large cuff was demonstrated.
3. Functional aspects of the tracheal mucosa (Papers IV and V); this part of the investigation concerned blood flow, both under normal conditions and under the influence of an inflated cuff, and the fluid balance.

Definitions

Airway pressure: The pressure within the trachea. Airway pressure is further described by the terms: end-inspiratory, end-expiratory, peak, and mean. Airway pressure caused by positive pressure lung inflation often influences tracheal wall pressure exerted by a tracheal cuff.

Aspiration protection: Prevention of contamination of the lower airway with liquid or solid particles. This does not necessarily imply prevention of bacterial contamination.

Cuff diameter: The outer diameter of a cuff which has been inflated at a pressure of 15 cm H_2O (11.1 mmHg) and allowed to deflate passively to a pressure of 1.0 cm H_2O (0.73 mmHg).

Cuff-to-tracheal wall pressure: That force per unit area (pressure) which is exerted upon the internal tracheal wall by the cuff at various sites. Cuff-to-tracheal wall pressure (C-T pressure) is further described by the terms; end-inspiratory, end-expiratory, peak, and mean. C-T pressure *SHALL* be measured at the anterior tracheal wall.

High-volume cuff: Synonymous to large cuff.

Inflating tube: The tube provided for inflating and deflating the tracheal tube cuff.

Large cuff: See cuff characteristics. (p. 13).

Large-resting-diameter cuff: Synonymous to large cuff.

Large-residual-volume cuff: Synonymous to large cuff.

Low-volume cuff: Synonymous to small cuff.

No-leak ventilation: The condition in which a preset, measured volume of gas is delivered to test lungs, or the lungs of a subject, and the same volume of gas is exhaled through the lumen of the tracheal tube. No gas leakage between the inflated cuff and the trachea shall occur during no-leak ventilation.

Pilot balloon: A balloon which may be fitted to the inflating tube to indicate inflation of the cuff.

Prestretch: A small plastic cuff is heated in boiling water. The cuff is overinflated, thereby distending the cuff wall in such a way that the small cuff is converted to a large cuff. The cuff is allowed to cool while still inflated.

Prolonged use: Any cuff or tube intended for use in a patient's trachea for a continuous period of about twenty-four hours or more is considered a device for prolonged use.

Residual volume: The volume of air which can be withdrawn from the cuff after it has been inflated at a pressure of 15 cm H_2O (11.1 mmHg) and allowed to deflate passively to a pressure of 1.0 cm H_2O (0.73 mmHg) and assume its natural shape in the air. This volume is measured at atmospheric pressure.

Resting diameter: See cuff diameter.

Shearing force: In this investigation this term is used to express the force causing mucosal damage by motion of the trachea relative to the cuff.

Slope pressure: That rise in pressure against a non-rigid simulated human tracheal wall which occurs when 1 ml of air is added to a cuff which has been inflated to the minimum pressure

producing no-leak ventilation at a peak airway pressure of 15 cm H_2O (11.1 mmHg) in an appropriate size trachea connected to a test lung.

Small cuff: See cuff characteristics. (p. 13).

Small-resting-diameter cuff: Synonymous to small cuff.

Small-residual-volume cuff: Synonymous to small cuff.

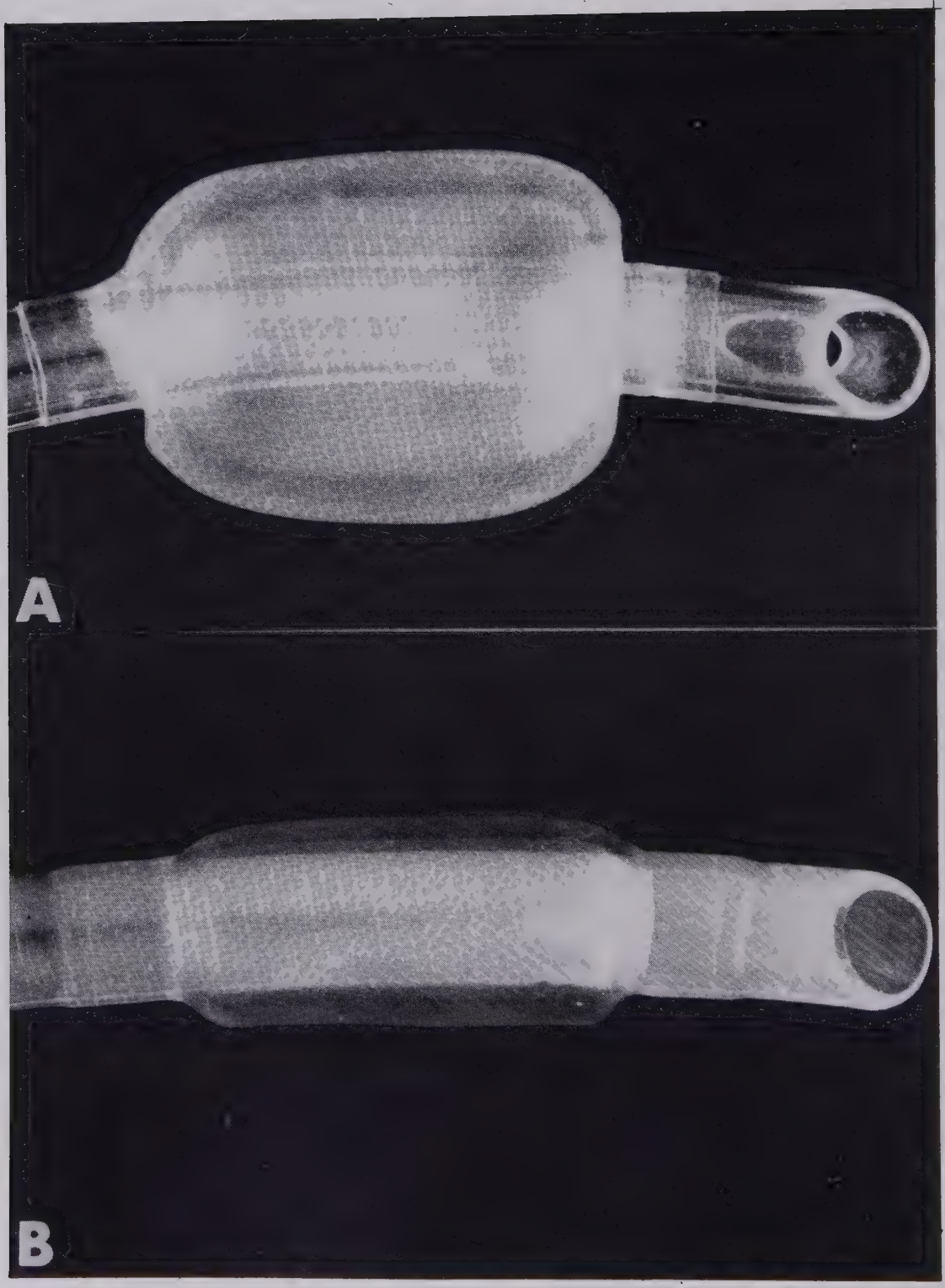
Tracheal cuff: A tracheal cuff is a seal which is used to prevent leakage of gases, liquids, or foreign material into or out of the trachea.

Cuff characteristics

	Large cuff	*Small cuff*
Cuff diameter:	Shall well exceed tracheal diameter.	Less than tracheal diameter.
Residual volume:	More than 30 ml.	3 – 6 ml.
Cuff wall:	Thin, pliable.	Thick, rigid.
Cuff pressure in relation C-T pressure:	Equal.	Different. Varying difference.
Cuff pressure when inflated so as to just reach tracheal wall:	Close to zero.	High. (75 – 200 mmHg).
C-T pressure needed for no-leak:	Low. 5 – 20 mmHg.	High and uncontrollable.
Cuff wall behaviour when cuff inflated to no-leak:	Not distended. Drapes freely over the tracheal wall. Lies in folds.	Distended Expands asymmetrically
Cuff pressure in relation to airway pressure:	Equal at any moment. Airway pressure is able to reduce the cuff volume by squeezing the pliable cuff wall facing the trachea.	No relation. Cuff wall too rigid.
Area of cuff in contact with trachea at no-leak:	Large.	Small.
Slope pressure:	Low.	Steep rise.

Summary

A large resting diameter in relation to the size of the trachea is a fundamental prerequisite for the ability of a cuff to seal in such a way that the intracuff pressure equals the C-T pressure. As soon as there is circumferential tension in the cuff wall, the C-T pressure no longer equals the intracuff pressure.



a. Large cuff.
b. Small cuff.

Material and methods

Rabbits were used for the experiments. Dogs would have been preferable in regard to size, but for cost reasons this was not possible.

Mostly white rabbits (New Zealand white strain) were employed, but seven grey rabbits (Dutch ram) were also used. The animals were of both sexes and weighed from 0.9—4.4 kg, the majority being about 2 kg.

The rabbits were anesthetized either with urethane 20 % in saline, in a dose of 1 g/kg body weight, or with 2 % sodium pentobarbital (Nembutal^{R}) in a dose of 50—60 mg/kg body weight. The anesthetics were administered by intravenous injection through an ear vein. The animals breathed spontaneously throughout the experiments.

Intubation, tube and cuff

Translaryngeal *intubation* was performed under direct observation with the aid of a specially made laryngoscope. Great care was taken to minimize tracheal damage from the intubation itself. At intubation the cuff was completely deflated in order to diminish shearing forces.

The intubation *tube* was made of PVC and was specially constructed (by Portex) for this project. The tube had an inner diameter (ID) of 2.5 mm and an outer diameter (OD) of 3.5 mm.

The *cuff* was prestretched in hot water by the author (cf. Geffin & Pontoppidan 1969), giving it large-cuff properties (Lomholt 1967, Carroll & Grenvik 1973, Carroll et al. 1974) in relation to the rabbit trachea. After prestretching, the resting diameter of the cuff was about 10 mm. The thickness of the cuff wall varied between 0.07 and 0.12 mm, depending upon the degree of prestretching.

In practice the cuff might fold and form six layers of cuff wall between the tube and the inner wall of the trachea. An extreme total OD, the deflated cuff included, could thus have reached $3.5 + (6 \times 0.12) = 4.22$ mm in these experiments. In addition, the elasticity of the cuff wall might have added a little to this extreme OD, so that in unfavourable circumstances it would have approached the ID of the trachea, which was about 5 mm. This should be borne in mind when interpreting the results. Radiography of the cuff site, however, showed a clear air gap between the tube and the tracheal wall, indicating that there was usually enough space in the trachea to accommodate the deflated cuff without undesired pressure on the tracheal wall.

The cuff pressure was continuously monitored via a Y-connector, with a mercury manometer, according to Cox & Schatz (1974).

Paper I
Surface structure and vascular anatomy of the tracheal wall under normal conditions and after intubation

U. Nordin, B. Engström, B. Jansson and C.-E. Lindholm

White rabbits were used to study the structure of the normal tracheal wall and to analyse the effect of a large tracheal tube cuff on the mucosa. The specimens were examined by direct observation, using a binocular preparation microscope (Wild M 5), and by phase contrast microscopy and scanning (SEM) and transmission (TEM) electron microscopy.

The *normal tracheal wall* was found to consist of a mucus membrane and a series of horse-shoe shaped cartilages of the same appearance as in the human trachea. The surface layer of the mucosa is built up of a *pseudostratified columnar ciliated epithelium* containing many goblet cells. This rests on a rather thick (1000 Å) basement membane, beneath which there is a loose network of connective tissue cells and fibers forming the lamina propria. In this layer there is a rich capillary network. The free upper surface of the cells is provided with large numbers of cilia.

Between the cilia there are numerous microvilli. The cilia are 6–7μm long and approximately 0.2 μm in diameter.

The goblet cells or mucus producing cells are quite different in appearance from the ciliated cells, being goblet-shaped with an upper widened portion and a slender foot. These cells form secretory granules which fill the upper, thecal portion of the cell. The free surface of the cells is often richly furnished with microvilli.

In this investigation the intubation time was kept constant at 15 min, while the C-T pressure was varied from an uninflated cuff to a pressure of 100 mmHg.

When the tube was placed in the trachea *without inflation of the cuff* it was quite clear that this was sufficient to cause minor superficial damage to the epithelial lamina. This damage only occurred over regions where a cartilage was situated. In the intercartilaginous regions no damage was seen.

When the cuff was inflated, it resulted in an increase of the mucosal damage, the extent of the injury being directly related to the pressure in the cuff. A gradual increase in C-T pressure thus led to progressive extension of the mucosal damage. This took the form of both widening of the injured areas and penetration of the damage to deeper regions. In the damaged regions there was extensive cell loss, the epithelium was sometimes almost completely absent and only scattered cells remained.

At a *C-T pressure of 100 mmHg* the damage afflicted almost the entire mucosa and only small undamaged mucosal regions remained. At this stage it appeared as if the basement membrane had also begun to disintegrate.

Paper II
Surface structure of the tracheal wall after different durations of intubation

U. Nordin, B. Engström and C.-E. Lindholm

White rabbits were used and the specimens were studied by the same methods as in paper I.

The aim of this investigation was to study tracheal damage caused by different durations of intubation, keeping the C-T pressure constant. By study I and the present investigation an attempt was made to answer the question of which is the most important factor in causing mucosal damage, the C-T pressure or the duration of intubation. Another aim was to create a model by which "standardized" tracheal damage of different degrees could be produced to allow a study of the regeneration of mucosa injured to a fairly well controlled depth. This study is in progress at present.

The time of intubation was varied between one and four hours. The results are presented in three different groups of C-T pressures, with variations of the intubation time within each group. The C-T pressure in the first group was fairly "normal", 20 mmHg, in the second group "medium", 50 mmHg, and in the third group "high", 100 mmHg.

A *C-T pressure of 20 mmHg* for *1 to 2 h* of intubation damaged the mucosa on top of the cartilages to such an extent that it was partly denuded almost down to the basement membrane. In intercartilaginous regions some of the cells had lost their cilia, but the interior of the cells seemed intact. The damage was not significantly greater than that after 15 min of intubation at the same pressure. At *3 h* of intubation the damage was more widespread and in the intercartilaginous areas the epithelium was partly compressed.

A *C-T pressure of 50 mmHg* for *2 h* of intubation destroyed most of the epithelial cells on top of the cartilages. The basement membrane was partly denuded but seemed intact. Again, the damage was not significantly greater than after 15 min of intubation with the same C-T pressure. At *4 h* of intubation some parts of the mucosa in the intercartilaginous regions consisted of low epithelial cells covered by microvilli. These cells were intermingled with normally ciliated cells. Whether this was an expression of incipient disintegration of the cilia or a sign of incipient cilial regeneration, only 4 h after the damage was made, cannot be answered at present. This question is being further elucidated in an investigation in progress at present (Nordin), where the regeneration of cuff-induced mucosal damages is being studied.

At a *C-T pressure of 100 mmHg* for *1 h* of intubation the whole part of the mucosa at cuff level was now damaged to some extent. Large areas of the basement membrane were denuded and in some areas it was completely absent, leaving the mucosal stroma visible. After *4 h* of intubation the mucosa covering the cartilages was sometimes destroyed down to the cartilage itself, and bacteria were found, for the first time, to be invading the damaged mucosa. This was the only time in all our experiments at which bacteria were observed. It thus seems that even with fairly penetrating damage, local infection does not begin to play a serious role until after about 4 h of intubation.

These investigations support the opinion of Mathias & Wedley (1974) that for "ordinary" periods of intubation, i.e. some hours, the C-T pressure is more important than the duration of intubation for the occurrence of tracheal damage. We are also convinced that in general the C-T pressure has greater *relative* importance for the degree of damage than the intubation time.

Paper III
The vessels of the rabbit trachea and ischemia caused by cuff pressure

U. Nordin and C.-E. Lindholm

In order to consider the possibility of using the rabbit as a test animal for studies of the capillary perfusion of the tracheal wall under physiological conditions and during translaryngeal intubation, and to visualize the effect of an inflated tracheal tube cuff on the vascular bed, we injected Microfil silicone rubber* (Compound MV 118 plus diluent and curing agent) intraarterially. When injected, the silicone rubber mixture is a fluid with a viscosity in the 15–25 centipoise range. If the curing agent is added immediately before injection, however, the silicone rubber is transformed in 15 minutes into an elastomeric gel, which fills the vessels and thus preserves their anatomy.

The rabbit was found to have large bilateral longitudinal arteries located outside the trachea and supplying the trachea and the esophagus. We have named them Aa tracheo-oesophageales longitudinales (the longitudinal tracheo-esophageal arteries) (Nordin). They have connections with the bronchial arteries in the mediastinum and are mainly supplied by a branch of the right subclavian artery. The main branch supplying the right longitudinal tracheo-esophageal artery also has wide anastomoses with the intercostal arteries. The main branch feeding the left longitudinal tracheo-esophageal artery crosses the trachea from right to left anteriorly. The longitudinal tracheo-esophageal arteries pass posterolaterally to the trachea in the groove between the trachea and the esophagus, giving off numerous segmental branches to both these organs. The longitudinal tracheo-esophageal arteries in the upper cervical region are supplied mainly by branches of the inferior thyroid arteries originating in the common carotid arteries. All longitudinally orientated vessels are interconnected and give off arcades of semicircular arteries, which pass submucosally between the tracheal cartilages. These intercartilaginous arcades are also connected with each other through the capillary bed of the mucosa covering the tracheal cartilages and through scattered small-caliber arterial shunts between one semicircular artery and an adjacent one.

In addition to the described vascular system, located mainly in the submucosa, there is a similar distribution of vessels close to the external surface of the trachea.

Our studies also disclosed a system of sinusoidal ectasias, or cavernous vascular spaces, as suggested by Sobin et al. (1963). These sinusoids, which are mainly located submucosally, lie in contact with small-caliber thin-walled vessels of the tracheal wall. They are lined with epithelium. It is probable that they play a role in the conditioning of inhaled air.

Translaryngeal intubation with a cuffed PVC tube was performed. The cuff had been sufficiently prestretched to obtain large cuff characteristics in relation to the rabbit's trachea. C-T pressures of 50 mmHg always hindered the silicone rubber perfusion of the capillary bed in the tracheal mucosa in contact with the cuff.

The conclusion drawn from this study was that the rabbit trachea has a rich vascular supply. The small arteries form a network of anastomoses in all three dimensions within the tracheal wall. The complexity of the arteriolar and capillary bed in the tracheal wall suggests that the rabbit trachea has a vascular bed very well prepared to resist a threat to its nutritive blood supply. This fulfils an important prerequisite for the use of the rabbit as a test animal for quantitative studies of the effect of an inflated cuff on the capillary perfusion of the tracheal wall.

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Paper IV

Transvascular fluid exchange in the tracheal mucosa

U. Nordin, Ö. Källskog, C.-E. Lindholm and M. Wolgast

This study was undertaken because it was considered of interest to ascertain the perfusion pressure in the rabbit tracheal mucosal capillaries, to obtain an idea about when the pressure of a tracheal tube cuff on the mucosa can be expected to stop the capillary blood flow, i.e. to cause local ischemia, with a consequent risk of tracheal damage and stenosis.

This study was also undertaken to evaluate the fluid balance in the tracheal mucosa, and is closely related to study V, which deals with the blood flow characteristics under normal conditions and after the insertion of the foreign body, (e.g. a tracheal tube) into the trachea. It was clearly evident from the latter investigation that this will cause an irritation of the mucosa, resulting in a release of a vasodilating agent which with the greatest probability exerts its effect on the small arteries and arterioles in the tracheal microvasculature. This was reflected by an increased blood flow. Such dilatation will also mean an increased pressure in the capillary bed, and it seems likely that this will enhance the outward filtration of fluid across the capillary wall into the mucosal interstitium, primarily in the proximal part of the capillaries. The generally increased pressure will also diminish the rate of reabsorption in the late segment of the capillaries and small veins in the submucosal region.

In order to perform the micropuncture experiments (see below), it proved essential to eliminate movements of the tissue that normally occur; e.g. movement of the trachea in the craniocaudal direction synchronous with breathing. In this series of studies the mucosa was exposed via a midline incision in the ventral part of the trachea. Two clamps were then attached to the edges and fixed to the operating table on both sides. With this technique the tissue could be immobilized to a sufficient degree in most cases.

In parallel with the micropuncture experiments the blood flow was analysed by the microsphere method (see below). Thus two series of experiments were carried out, comprising 1) studies of the mucosal blood flow and 2) micropuncture investigations. The trachea was prepared and fixed in the same way for both series.

Series 1: Blood flow investigations.

The microsphere technique was used for determining the capillary blood flow in the tracheal mucosa. The microspheres (see below) were administered through a catheter placed in the left ventricle. A catheter in the left femoral artery was connected to a suction pump, which sampled at a constant rate of 0.82 ml/min. The microspheres (141-Ce labelled and 85-Sr labelled 3M microspheres, St Paul, Minn., USA), numbering about 1 million, were suspended in 0.6 ml of rabbit plasma. For each determination of mucosal blood flow 0.6 ml of the plasma-microsphere suspension was injected through the catheter into the left ventricle. During the injection, and up to 1 min afterwards, blood was drawn continuously from the left femoral artery at a constant rate of 0.82 ml/min.

It may be assumed that the injection of the microsphere plasma suspension into the left ventricle will ensure complete mixing of the microspheres. The microspheres, which are 15 μm in diameter and homogeneously suspended in the

blood, will be carried by the blood to the different organs where they will be trapped in the capillary bed. The number of spheres trapped in different tissues will be directly proportional to the blood perfusion of that particular tissue during the time of injection. The first injection, as a rule with the 141-Ce labelled microspheres, was given under resting conditions, i.e. when the trachea was still intact. The second injection, with 85-Sr labelled microspheres, was given after the trachea had been exposed and fixed with the clamp arrangement described above. Pieces of the trachea in the region accessible for micropuncture, as well as from the region cranial and caudal to this site, were then freed by blunt dissection from the underlying perichondrium at the site of the tracheal cartilages, and from the annular ligaments between the cartilages, with the aid of an operation microscope. With this mode of dissection the tissue pieces contained the mucosa, in which, in accordance with the Nomina Anatomica, we include the tela submucosa. The radioactivities of the tissue pieces and blood sample were determined.

For calculating blood flow the formula $F/M = F_s/M_s$ was used, where F is the blood flow to the region in question, M the activity of the isotope, F_s the blood sampling rate of 0.82 ml/min and M_s the radioactivity in the blood sample. Cardiac output was determined from the same formula, replacing the factor M by the total amount of radioactivity injected; the factor F is now the cardiac output.

The mucosal blood flow in the region used for the micropuncture experiments was estimated at 0.62 ± 0.41 ml/min · g tissue in the resting state. Essentially the same values were obtained for the areas cranial and caudal to this region. After the manipulation of the trachea the blood flow increased markedly to 3.22 ± 1.55 ml/min · g, and a similar increase was noted for the areas cranial and caudal to the region used for micropuncture. It is thus clear that the manipulations of the trachea induced an arteriolar dilatation in the same way as on introduction of a foreign body. The figures obtained in the micropuncture experiments will thus not apply to normal conditions but to the conditions of an irritated mucosa.

Series 2: Micropuncture investigations.

The experiments with the micropuncture technique aimed at exploring the microanatomy of the tracheal mucosal vascular bed and interstitium, and also at measuring the hydrostatic and colloid osmotic pressures and the fluid turnover. Injection of dyes allowed identification of the early and late part of the capillaries as well as the venules. It was found that the capillary network was oriented longitudinally in the layer below the tracheal epithelium. The network was freely anastomosing and supplied with several arterioles. It was drained by typical interconnecting vessels, which formed a loop from the superficially located true capillaries to the dense network of sinusoidal veins in the submucosal region. These "venules" increased in size as they passed down to the submucosal veins. The most prominent feature of the mucosal vasculature was the very dense net of sinusoidal veins in the submucosal region, which again was freely anastomosing. Somewhat larger veins draining the network could also be identified. The region between the capillaries and the layer beyond was occupied to a surprisingly large extent by a very richly developed lymphatic system. The lymphatic tree ended in sac-like structures which were designated terminal lymphatic sacs. The capillaries, venules and submucosal veins were all permeable to the dye. Thus when the dye was injected the greatest part followed the blood stream but some of it diffused out into the interstitium and then returned to the blood stream. This process was complete within a few seconds. Concerning the lymphatic system, the connecting lymph ducts proved to be fairly impermeable to the dye, the only site of passage being the above-mentioned terminal lymphatic sacs. The dye injected into the interstitium was first collected by the walls of the lymphatic sacs and then passed into the collecting lymphatic channels; this process was fairly slow, with a turnover time of about $\frac{1}{2}$ hour.

The hydrostatic pressures within the microvasculature were investigated by means of sharpened glass capillaries with a tip diameter of 2-4 μm. These were attached to the servo-nulling device of Wiederhielm (1964) in a modification by Intaglietta et al. (1970). The early part of the

capillaries was denoted as the first branch distal to an arterial branch, the latter being seen as a red dot which split up into a capillary network. The mid-capillary pressure is in fact not the pressure at the mid-part of the capillary but the average pressure of randomly punctured capillaries. The late part of the capillary is easily identified as the part in the immediate vicinity of the venules described above. The capillary pressure decreased from 28 mmHg in the early part of the capillary to 17 mmHg in the mid-part and about 14 mmHg in the late part. The pressure in the sinusoidal submucosal veins was 12 mmHg. The pressure in the interstitium and terminal lymphatics was 3-4 mmHg.

The colloid osmotic pressure in plasma was determined from the protein concentration in systemic blood and was found to be 6.1 $\pm$ 0.2 %. The protein concentration in the interstitial fluid or lymph fluid was 5.7 $\pm$ 0.8 %, as obtained from small samples withdrawn by sharpened glass capillaries with an outer tip diameter of about 10 μm. The sample volume was fairly high—about 50 nl or more. The colloid osmotic pressures would then be 21 mmHg and 19 mmHg in plasma and interstitial fluid, respectively. At these values there would be an outward filtration of fluid from all the vascular structures, i.e. both from the capillaries and from the sinusoidal submucosal veins. The driving force was 22 mmHg in the early part of the capillary, decreasing to 6 mmHg in the venous plexus. The most remarkable finding in this context was the high colloid osmotic pressure, of 19 mmHg, in the interstitium. This will reflect a heavy leakage of proteins through the capillary membrane. The transfer sites could be either large pores or a pinocytotic process; the present experimental set-up will not allow a more detailed evaluation of the transfer route.

The transport of plasma proteins was investigated in an additional study in which labelled albumin was injected into the systemic circulation and a series of interstitial fluid samples was obtained from time zero up to 2 h after the injection. A transit time of about 45 min was noted. The short time of 45 min will thus reflect a very high rate of transport of the proteins. It is thus concluded that the fluid entering the interstitium will be composed of a protein free filtrate, most probably passing through a small pore system. In addition there will be a comparatively high outflow of proteins. The final concentration of proteins in the filtrate will not necessarily equal that in the interstitium.

From the above results it is suggested that the interstitial fluid is drained by two separate routes. Part of the fluid will be reabsorbed by the secretory glands for the production of mucus. This part is essentially a protein-free fraction, as the protein concentration in the mucus is essentially nil. Due to this process the protein concentration in the interstitial fluid will increase, which is probably the explanation for the very high concentration of proteins in the interstitium of 5.7 %. The drainage of this part of the fluid will occur through the terminal lymphatic sacs into the collecting lymphatics.

The process described seems to suit the demands on the tracheal mucosa of an increased production of mucus in the case of introduction of a foreign body. Thus the foreign body will cause an irritation of the mucosa, resulting in release of a histamine-like substance or an equivalent vasodilator agent. The dilatation of small arteries and arterioles will obviously lead to an increased blood flow but also to increased pressures in the mucosal microvasculature. The high blood flow and the high pressures will favor the outward filtration of fluid to supply the secretory glands with increased amounts of fluid to be secreted. The high rate of mucus production will assist the trachea in its attempt to remove a foreign body which has originally caused this reaction. The question then arises if there is any need for a higher rate of protein transport. From the point of view of the secretory glands plasma proteins will be unnecessary, for the simple reason that mucus is essentially protein-free. It could, however, make sense with respect to antibody proteins, which will now gain access to the mucosa. It has been shown, in fact, that in the case of allergic reactions there is an increase in the protein concentration in the mucus (though only trace amounts), especially the concentration of IgE (Deuschl & Johansson, 1977).

It is evident, however, that the disturbed fluid balance described here will mean a great risk of edema in the tracheal mucosa. It must be pointed out that in the present studies the rabbits lay in a horizontal position, which explains the fairly high pressure of 12 mmHg in the venous system. It is well known (Jonson & Rundcrantz, 1969) that this pressure will decrease towards zero on changing from a recumbent to an upright position. This will obviously lead to a decreased pressure within both the capillary and the venous system by about 12 mmHg. In this case, and assuming all other factors to be constant, the evaluation of the Starling forces shows that only the early part of the capillaries will allow an outward filtration of fluid, whereas the well-developed venous network reabsorbs the fluid. The hydrostatic pressure within the interstitium will thereby decrease. The drainage of interstitial fluid through the lymphatic channels will also be favored in an upright body position, since the pressure in these channels will also be decreased.

In conclusion, any irritation of the mucosa will lead to a situation with a great risk of tracheal mucosal edema. With a patient in an upright body position this edema will be less but in a recumbent position the risk is much greater.

As pointed out above, the present results all refer to an irritated mucosa. It is probable that under normal resting conditions the resistance of the small arteries and arterioles will be greater, resulting in a reduction of the capillary pressures. The leakage of protein from the vascular system will probably also be less; in the experiments in which the mucosa was treated more gently the interstitial protein concentration tended to be lower. A decreased pressure in the capillaries and a decreased colloid osmotic pressure in the interstitium will both serve to diminish the filtration out of the early part of the capillaries and to increase the reabsorption in the late part of the capillaries and the dense venous network. In this case there will be no risk of edema either in the upright or in the recumbent body positions.

Paper V

Blood flow in the rabbit tracheal mucosa under normal conditions and under the influence of tracheal intubation

U. Nordin, C.-E. Lindholm and M. Wolgast

The microsphere technique described in paper IV was used to study the influence of a large tracheal tube cuff on the capillary blood flow in the rabbit tracheal mucosa.

The investigations were divided into three series:

Series 1 was a control series of 10 rabbits, in which the tracheal mucosa was left untouched, i.e. the animals were not intubated.

The two determinations with 141-Ce and with 85-Sr were performed with an interval of 15 min, i.e. both determinations were made under control conditions.

Series 2 consisted of 8 rabbits, in which the 141-Ce injection was given without intubation and the 85-Sr injection was given after the insertion of an endotracheal tube, which was left uninflated for 15 min before injection.

Series 3 consisted of 45 rabbits, in which the first injection (141-Ce) was given after the insertion of an endotracheal tube without inflation of the cuff, and the second injection (85-Sr) was given when the cuff had been inflated to a pressure varying from 10 to 120 mmHg for 15 min.

In the control series (1), the mucosal blood flow was about 0.3 ml/min and g tissue. The cardiac output at the first microsphere injection was 164 $\pm$ 41 ml/min and kg body weight (mean $\pm$ s.d.), and that at the second injection was slightly lower, i.e. 142 $\pm$ 52 ml/min and kg body weight.

After the insertion of the tube without inflation of the cuff, the mucosal blood flow in series 2 showed a marked increase, as a result of reactive hyperemia, whereas the cardiac output remained essentially unchanged.

This is reflected by the high blood flow values found under control conditions in series 3 (Fig. 1). In this study, the mean value of 45 determinations was 3.4 ml/min · g, i.e. the reactive hyperemia caused a more than tenfold increase in the blood flow.

The influence of the cuff pressure on the mucosal blood flow is also evident in Fig. 1. It can be seen that the mucosal blood flow decreased with increasing cuff pressure, approaching zero at pressures in the range of 120—130 mmHg. This relation between mucosal blood flow and increasing cuff pressure is statistically significant (see Fig. 1), as calculated by paired analyses. The cardiac output was fairly constant throughout the experiment in series 3.

To further analyse the relation between blood flow and cuff pressure, the fractional change occurring on induction of different pressures is plotted against perfusion pressure (Fig. 2); this was calculated arbitrarily as the difference between systemic blood pressure and cuff pressure and expressed as a percentage of the original perfusion pressure. It should be emphasized, however, that the perfusion pressure thus calculated does not necessarily represent the true perfusion pressure; the latter will rather be the difference between the pressure in the small arteries supplying the trachea with blood and the pressure in the venous plexuses of the mucosa. Keeping this limitation in mind, Figure 2 shows that for a small increase in cuff pressure the blood flow is reduced proportionately more than the reduction in perfusion pressure. This discrepancy could, however, easily be ex-

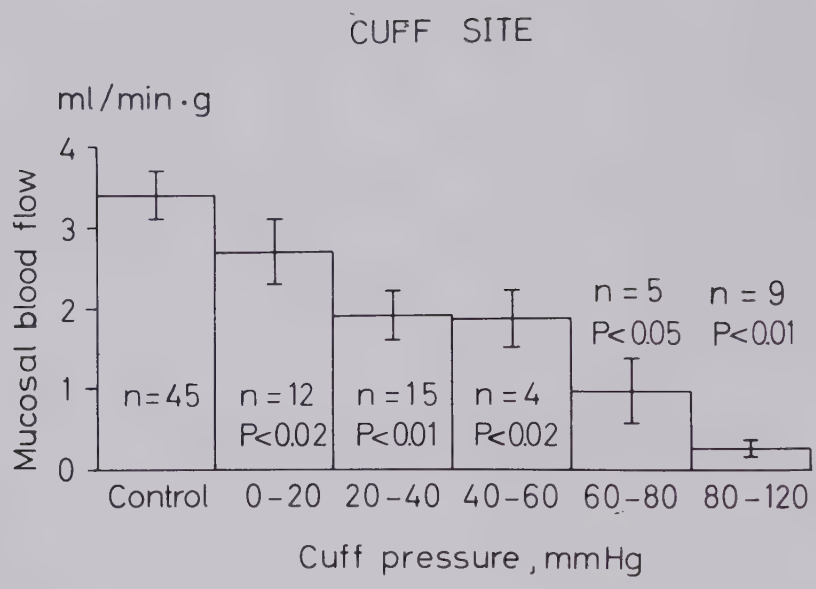

Fig. 1. Mucosal blood flow under control conditions, i.e. with the tube inserted but with no inflation of the cuff, and the flow during different cuff pressures, which are grouped here in steps of 20 mmHg. It is seen that the flow decreases with increasing cuff pressures, approaching zero at cuff pressures of 80—120 mmHg, i.e. at pressures corresponding to the systemic arterial pressure.

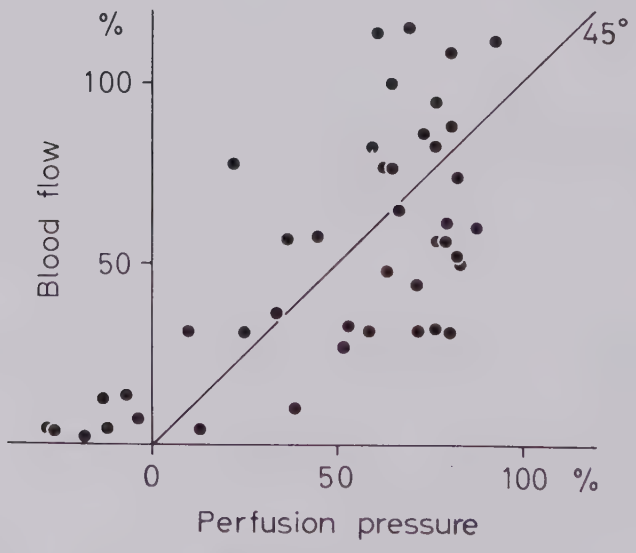

Fig. 2. Relation between the tracheal mucosal blood flow, expressed here as a percentage of that under control condition (ordinate), and the "perfusion pressure" (abscissa), calculated as the difference between systemic arterial pressure and cuff pressure, and expressed as a percentage of that under control conditions (see text). Even when the calculated perfusion was zero or negative there was still some blood passing through the tracheal mucosa. The calculated perfusion pressure was thus not identical with the true perfusion pressure. The reason for this was probably that the large cuff used in these experiments did not have ideal properties. The discrepancy from the ideal state was, however, quite small.

plained as being due to errors in the estimation of the true perfusion pressure. In the case of high cuff pressures it is evident that there was still some blood flow in the mucosa in spite of a zero or even negative perfusion pressure. It is reasonable to explain this finding by assuming that in some places the cuff pressure was not evenly transmitted to the vascular structures, i.e. the pressure exerted by the cuff in some places was lower than the intracuff pressure. This would then indicate that the large cuff used does not function as an "ideal" large cuff (see "General discussion", p. 26, for details).

General discussion

It seems quite clear from this investigation that any intubation causes a certain amount of surface damage to the tracheal mucosa, no matter how short its duration, or how low the C-T pressure. This vulnerability of the mucosa was indicated from the early experiments of Hilding (1952), and our finding is in accordance with the observations of Klainer et al. (1975).

An increase in C-T pressure will lead to progressive extension of the mucosal damage. The basement membrane comprises an important protective layer against deep ulceration. Thus in the present studies it was not disintegrated until a C-T pressure of about 100 mmHg was applied, if the time of intubation was kept at only 15 minutes. When the same C-T pressure was exerted for four hours, on the other hand, the mucosa covering the cartilages was sometimes destroyed down to the cartilage itself.

It was obvious that the damage began and was most pronounced at the mucosa covering the tracheal cartilages. This is explained by the fact that the wall of the cuff used was not sufficiently thin and pliable in relation to the smallness of the rabbit trachea. This emphasizes the importance of the *quality of the cuff wall*. The thicker and more rigid it is, the more will the cuff act as a small-volume type, i.e. it will ride on the edges of the cartilages, where it will cause deep ulceration. This will happen even if the resting diameter of the cuff is large enough to provide it with large-cuff properties in relation to the trachea.

It must also be underlined that the *large resting diameter* of the cuff is the crucial factor in allowing the cuff to seal in such a way that the intracuff pressure will equal the C-T pressure. It must be kept in mind, on the other hand, that the large resting diameter of the cuff will also allow high intracuff pressures to be transmitted undiminished to the tracheal wall until such time as the diameter of the trachea exceeds the diameter of the cuff, when *circumferential tension within the cuff* will start to limit the effective C-T pressure. At such a time, the trachea is already dilated, and the physics of seal is changed from that of the large cuff to that of the small (high pressure) cuff. It is thus important to control the intracuff pressure and the resulting tracheal diameter.

When the length of intubation was extended to two hours, the damage was not significantly greater than that seen after 15 minutes of intubation at the same C-T pressure. Our findings are thus in accordance with the report by Mathias & Wedley (1974) that for "ordinary" periods of intubation, i.e. some hours, the C-T pressure is more important than the duration of intubation for the occurrence of tracheal damage. We are also convinced that in general the C-T pressure has greater *relative* importance for the degree of damage than the intubation time.

When a foreign body, e.g. a tracheal tube, is inserted in the trachea, this causes a steep increase in the blood flow through the tracheal mucosa. This increase would seem to have a dual purpose:

1. It causes an enhanced outward filtration of fluid across the capillary wall into the mucosal interstitium. Part of this fluid will be reabsorbed by the secretory glands for the production of mucus. The *high rate of mucus production* will assist the trachea in its attempts to *remove* the foreign body which originally caused the reaction.

The irritation of the mucosa will also cause a heavy leakage of proteins through the capillary membrane into the interstitium. This will result in a raised colloid osmotic pressure, which will disturb the fluid balance, giving a great *risk of edema* in the tracheal mucosa.

This risk will be *diminished,* however, on changing the body posture from a recumbent to an *upright position,* as this will lead to a decreased pressure within both the capillary and the venous system (Jonson & Rundcrantz, 1969).

2. When the organism reacts to the presence of a foreign body with local hyperemia, this probably is a way of meeting a possible threat to its nutritive blood supply. This must play an important role in diminishing the effects of local mucosal ischemia caused by an inflated small tracheal tube cuff.

On the basis of our findings the different effects of a small and an *ideal* large cuff on the mucosal blood perfusion may be analysed in a *theoretical model* of the trachea. The *ideal* large cuff has very thin and pliable walls, which drape freely over the mucosa, allowing the C-T pressure to be transmitted to the mucosa overlying the cartilages, as well as to the mucosa over the intercartilaginous spaces. The pressure upon the mucosa trapped between cuff and cartilage may be somewhat higher than that on the intercartilaginous mucosa, where the force is dissipated in a relatively freely distensible tissue. But the more ideal the cuff, the more this relative pressure difference will be diminished. It is probable, further, that even on slight dilatation of the trachea, caused by the cuff, the annular ligaments

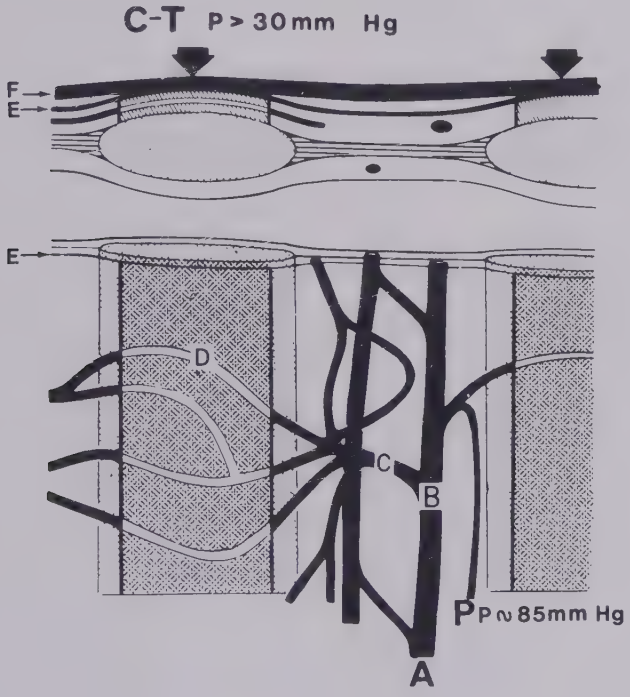

Fig. 1. The effect of a small cuff on the blood perfusion. Pressure is exerted mainly on the mucosa covering the cartilages (shaded). C-T pressures (see text) exceeding 30 mmHg will impede the capillary perfusion in this region. Pp perfusion pressure at **B.** (**E** = mucosal epithelium, **F** = cuff wall).

between the cartilages will start to back the mucosa, which will contribute to reducing the above-mentioned pressure difference.

Figure 1 shows a schematic drawing of the vascular anatomy of the trachea. At A in the figure, an artery is passing between the tracheal cartilages, to form an arteriole at point B. The arterioles then split up into a capillary network. Some of these capillaries supply the mucosa between the cartilages, while others traverse the mucosa, covering the cartilages. The mean systemic blood pressure in the experimental series was about 95 mmHg (point A).

At branching point B the pressure was estimated to be about 85 mmHg. The arteriolar pressure, as measured by micropuncture techniques in study IV, was 30 mmHg and the mean pressure within the capillary network was 20 mmHg. The micropuncture experiments also showed that blocking of a single capillary with a small glass rod led to a pressure increase in the capillary to 30 mmHg, which is equal to the pressure at the branching point (C) proximal to the site of puncture (D). Similarly, when the arteriole was blocked at C, the pressure proximal to the blocking point rose to about 85 mmHg, i.e. to the pressure at branching point B.

When the information obtained in papers IV and V is applied to a *theoretical model* of the trachea, to examine the effects of a small cuff and an *ideal* large cuff, the following circulatory events can be expected.

In the upper part of Figure 1 the effect of a small cuff is illustrated schematically. The cuff wall is thick and unpliable, i.e. it exerts its pressure only on the mucosa covering the cartilages, leaving the intercartilaginous mucosa intact.

When the pressure from the cuff exceeds 20 mmHg, the capillaries at D in Figure 1 are blocked. This leads to an increase in the perfusion pressure to 30 mmHg, i.e. to the pressure at the proximal branching point C, and the blood perfusion is maintained. When the pressure from the cuff exceeds 30 mmHg, and the capillaries are again blocked, there will be no further increase in the perfusion pressure, as the arteriole is not compressed by the cuff, being drained through the capillaries located between the cartilages and thus untouched by the cuff. This means that when the pressure from the cuff exceeds 30 mmHg, local ischemia will occur in the mucosa covering the cartilages (shaded region in Fig. 1). This is in accordance with our clinical observations that the small cuff causes ulceration of the mucosa covering the cartilages.

In the upper part of Figure 2 the effect of an *ideal* large cuff is illustrated. The cuff completely drapes the inside of the trachea and exerts almost the same pressure over the entire mucosa. A C-T pressure of 20 mmHg blocks the capillaries at D. The perfusion pressure is raised to 30 mmHg, and the blood flow continues. When the C-T pressure exceeds 30 mmHg, the arteriole (C) is also blocked, since in this case the arteriole is not drained by the capillaries located between the cartilages, as these themselves are blocked by the cuff. This means that with rising C-T pressure, the perfusion pressure will also be increased and will be propagated further out into the capillary bed. *Theoretically*, not until the C-T pressure exceeds about 85 mmHg, i.e. the pressure at point B, will complete ischemia develop, and this will involve the entire mucosa.

Thus when the *ideal* large cuff exerts a C-T pressure exceeding 20—30 mmHg, the blood flow perfusion in the mucosa will be considerably decreased, but on the other hand the nutritive blood flow will not completely stop until C-T pressures far exceeding 30 mmHg are reached. Thus the tracheal vascular supply seems to have an inbuilt mechanism which tends to preserve a certain blood perfusion, even in the mucosa covering the cartilages, when pressure is exerted by a large-volume cuff, at least for short periods of time.

This adds to our understanding of why large cuffs seldom cause a clinically significant mucosal necrosis upon brief use of fairly high C-T pressures. It has been shown by Stanley et al. (1974) and Stanley (1975) that nitrous oxide will diffuse into a cuff filled with air during nitrous oxide-oxygen anesthesia and cause a pressure increase. Further, Revenäs & Lindholm (1976) reported that C-T pressures far exceeding 30 mmHg are commonly found after some hours of this anesthesia, but in spite of this, clinically

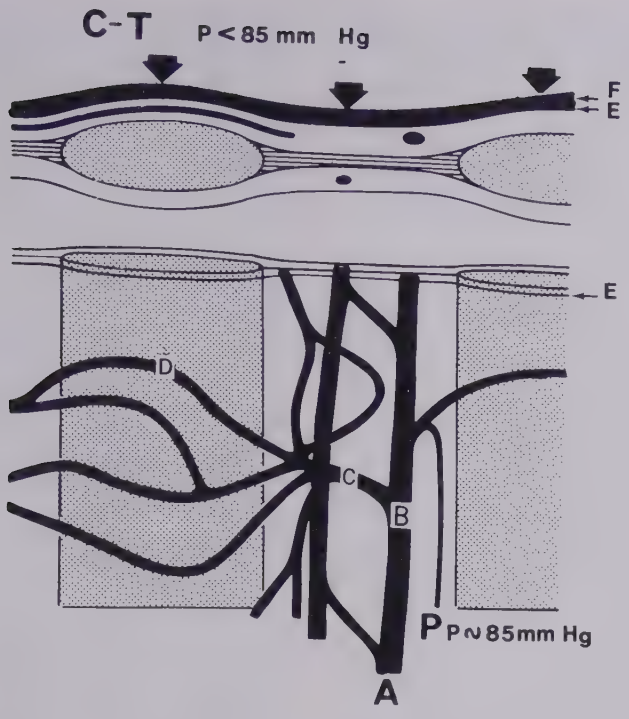

Fig. 2. The effect of a large cuff on the blood perfusion. Here pressure is exerted evenly over the entire mucosa draped by the cuff. The blood perfusion will not cease completely until the C-T pressure exceeds 85 mmHg (see text for details). Pp perfusion pressure at **B**. (**E** = mucosal epithelium, **F** = cuff wall).

significant tracheal wall damage has rarely been reported since the introduction of the large cuff.

If, during nitrous oxide-oxygen anesthesia, extremely high C-T pressures (in the range of 50—100 mmHg) are exerted over a period of some hours, it is only natural that the large cuff will then cause more sore throats than the small cuff, as remarked by Loeser et al. (1976). The thinner and the more pliable the cuff wall relative to the tracheal mucosa, the greater the surface area upon which this very high sealing pressure is distributed, which means that under this unfavourable condition the large cuff will damage a larger area of the trachea than a small cuff.

However, poor cuff pressure control is to be blamed for this damage rather than the large cuff itself. If the large cuff is inflated with the same anesthetic gases as are used for the anesthesia, the C-T pressure will be kept essentially unchanged during the course of the anesthesia.

Moreover, measurement of the intracuff pressure (=C-T pressure), at least when the cuff is being inflated, is the best guarantee for a safe cuff seal in the trachea.

The so called parachute cuff is a way of avoiding dangerous overinflation of the cuff that may occur either by a mistake on the part of the staff or by diffusion of nitrous oxide into the cuff during nitrous oxide-oxygen anesthesia. This cuff was first described by Martinez (1964) and Jackson & Rokowski (1967). The first one that seems to have provided a good seal, however, is that described by Merav (1971).

The parachute cuff has holes in the part of its wall that faces the bronchial tree. The airway pressure will be propagated through these holes and will thus inflate the cuff to exactly the pressure needed for sealing, but no higher. This means that the staff will not need to inflate the cuff through a special inflation tube. Neither will the cuff

pressure need to be monitored. As the cuff functions as an open system, there is no risk of an undesired pressure increase through diffusion of nitrous oxide into the cuff.

The disadvantage of the parachute cuff is its inability to prevent aspiration when the airway pressure, at the end of an exhalation, is zero or even negative.

In a preliminary report Nordin & Lyttkens (1976) described a modified parachute cuff which, if used with a respirator set at a positive end-expiratory pressure (PEEP), both provided a seal and protected against aspiration. This cuff has an increased length, extending up into the larynx, which prevents pooling of secretions above the cuff and will give a greater sealing area against the tracheal mucosa. The cuff has now been tested further on dogs and a full report is under preparation (Nordin & Lyttkens). The cuff always provided a seal. A PEEP of 7–10 cm H_2O gave full protection against aspiration, as tested by oral instillation of contrast medium under fluoroscopic control.

If this cuff is applied outside a standard large cuff, aspiration can always be prevented. If the PEEP disappears, e.g. on suction through the tube, the first measure is to suction the mouth clean. The inner cuff is then inflated in the usual way and full protection against aspiration will be achieved. During mechanical ventilation with PEEP, the inner cuff should be deflated, so that it does not block the holes in the walls of the outer cuff. The modified parachute cuff is especially suitable for use with high-frequency positive-pressure ventilation.

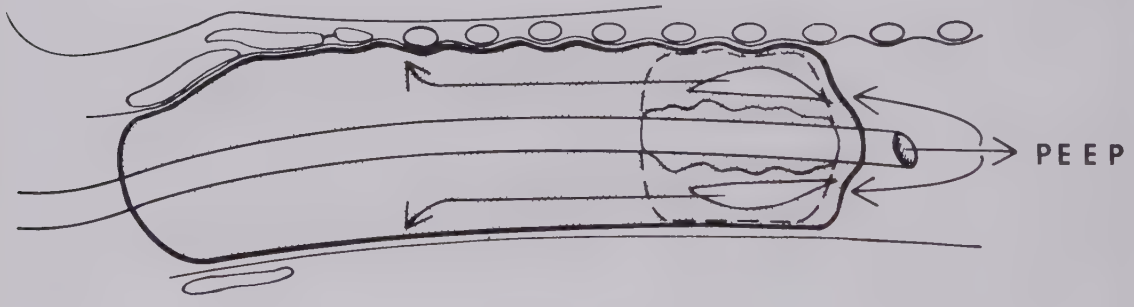

Fig. 3. Modified parachute cuff.

General conclusions

1. Any intubation causes a certain amount of surface damage to the tracheal mucosa.
2. Tracheal cuff damage is highly influenced by the product of C-T pressure and duration of intubation.
3. Of these factors, C-T pressure has the greatest importance.
4. Any irritation of the tracheal mucosa or disturbance of the mucosal lymph drainage will lead to a great risk of mucosal edema, and also favour a higher rate of mucus production, which will assist the trachea in its attempt to remove a foreign body that has originally caused this reaction. The risk of mucosal edema will be lower with the patient in an upright position.
5. A small cuff will stop the microcirculation in the mucosa covering the tracheal cartilages at C-T pressures as low as 30 mmHg.
6. A large cuff with thick and rigid walls will tend to produce lesions similar to those caused by a small cuff.
7. An *ideal* large cuff would considerably decrease the blood perfusion rate above C-T pressures of 30 mmHg, but on the other hand it would not completely stop the capillary blood perfusion of the tracheal mucosa until C-T pressures far exceeding 30 mmHg were reached. No cuff, however, has this property and we cannot therefore give general figures for a safe C-T pressure range, as this will vary with the quality of the cuff.
8. Although there are physiological mechanisms which preserve some microcirculation even at fairly high C-T pressures when an *ideal* large cuff is used, the C-T pressure should be kept below 20 mmHg. Pressures above this level may be regarded as not being catastrophic for a limited time period but should absolutely not be abused. Monitoring of the cuff pressure is therefore strongly recommended.
9. The walls of the *ideal* large cuff should be as thin and flexible as possible, so that it will drape evenly over the mucosa. The best guarantee for maintaining a satisfactory blood flow along the entire mucosa and for preventing a risk of local ischemia would be that the cuff wall should be so thin as to be almost non-existent, thus as nearly as possible giving the cuff the quality of an air cushion.

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References

Bryce, D.P., Briant, T.D.R. & Pearson, F.G. 1968. Laryngeal and tracheal complications of intubation. *Ann Otol 77,* 442.

Carroll, R.G. & Grenvik, Å. 1973. Proper use of large diameter, large residual volume cuffs. *Crit Care Med 1,* 153.

Carroll, R.G., Hedden, M. & Safar, P. 1969. Intratracheal cuffs: performance characteristics. *Anesthesiology, Vol. 31,* No 3.

Carroll, R.G., McGinnis, G.E. & Grenvik, Å. 1974. Performance characteristics of tracheal cuffs. *Int Anesthesiol Clin, Vol. 12,* No 3, p. 111.

Ching, N.P., Ayres, S.M., Paegle, R.P., Linden, J.M. & Nealon, T.F. 1971. The contribution of cuff volume and pressure in tracheostomy tube damage. *J Thorac Cardiovasc Surg 62,* 402.

Cooper, J.D. & Grillo, H.C. 1969. Experimental production and prevention of injury due to cuffed tracheal tubes. *Surg Gynec Obstet 129,* 1235.

Cooper, J.D. & Grillo H.C. 1969. The evolution of tracheal injury due to ventilatory assistance through cuffed tubes. *Ann Surg 169,* 334.

Cox, P. & Schatz, E. 1974. Pressure measurements in endotracheal cuffs: a common error. *Chest 65,* 84.

Deuschl, H. & Johansson, S.G.O. 1977. Specific IgE antibodies in nasal secretion from patients with allergic rhinitis and with negative or weakly positive RAST in the serum (Submitted to Clinical Allergy.)

Dunn, R.C., Dunn, D.L. & Moser, K.M. 1974. Determinants of tracheal injury by cuffed tracheostomy tubes. *Chest 65,* 128.

Eisenmenger, V. 1893. Zur Tamponade des Larynx nach Prof. Maydl. *Wien Med Wochenschr 5,* 199.

Geffin, B. & Pontoppidan, H. 1969. Reduction of tracheal damage by prestretching of inflatable cuffs. *Anesthesiology 31,* 462.

Grillo, H.C. 1970. Surgery of the trachea. *Current problems in surgery, p. 3,* Year book medical publishers, Inc., Chicago.

Grillo, H.C., Cooper,. J.D., Geffin, B. & Pontoppidan, H. 1971. A low pressure cuff for tracheostomy tubes to minimize tracheal injury—a comparative clinical trial. *J Thorac Cardiovasc Surg 62,* 898.

Grimm, J.E. & Knight, R.T. 1943. An improved intratracheal technic. *Anesthesiology 4,* 6.

Hedden, M., Ersoz, C.J. & Safar, P. 1969. Tracheoesophageal fistulas following prolonged artificial ventilation via cuffed tracheostomy tubes. *Anesthesiology 31,* 281.

Hilding, A.C. & Hilding, J.A. 1952. Tolerance of the respiratory mucous membrane to trauma: surgical swabs and intratracheal tubes. *Ann Otol 71,* 455.

Intaglietta, M., Pawula, R.F. & Tompkins, W.R. 1970. Pressure measurements in the mammalian microvasculature. *Microvasc Res 2,* 212.

Jackson, R.R. & Rokowski, W.J. 1967. An endotracheal tube with a cellophane cuff. *Arch Surg (Chicago) 94,* 160.

Jonson, B. & Rundcrantz, H. 1969. Posture and pressure within the internal jugular vein. *Acta Otolaryngol (Stockh) 68,* 271.

Kamen, J.M. & Wilkinson, C.J. 1971. A new low-pressure cuff for endotracheal tubes. *Anesthesiology 34,* 482.

Klainer, A.S., Turndorf, H., Wu, W-H., Maewal, H. & Allender, P. 1975. Surface alterations due to endotracheal intubation. *Am J Med Vol. 58,* 674.

Lauria, J.I. & Andersen, M.N. 1969. Automatically inflated cuffed tube for ventilatory support. *Rev. Surg 26,* 75.

Lindholm, C-E. 1969. Prolonged endotracheal intubation. *Acta Anaesthesiol Scand Suppl XXXIII.*

Loeser, E.A., Orr, D.L., Bennett, G.M. & Stanley, T.H. 1976. Endotracheal tube cuff design and postoperative sore throat. *Anesthesiology, Vol. 45, No 6,* 684.

Lomholt, N. 1967. A new tracheostomy tube: Cuff with controlled pressure on the tracheal mucous membrane. *Acta Anaesthesiol Scand 11,* 311.

Lomholt, N. 1971. A new tracheostomy tube. *Acta Anaesthesiol Scand Suppl 44.*

MacIntosh, R.R. 1943. Self-inflating cuff for endotracheal tubes. (A letter reporting the invention of W.W. Mushin.) *Br Med J 2,* 234.

Martinez, H.E. 1964. An improved cuffed tracheostomy tube for use with intermittent positive pressure breathing. *J Thorac Cardiovasc Surg Vol. 47,* 404.

Mathias, D.B. & Wedley, J.R. 1974. The effects of cuffed endotracheal tubes on the tracheal wall. *Br J Anaesth 46,* 849.

McGinnis, G.E., Shively, J.G., Pattersson, R.L. & Magovern, G.J. 1971. An engineering analysis of intratracheal tube cuffs. *Anesth Analg (Cleve) 50, No 4,* 557.

Merav, A.D. 1971. Low-pressure "parachute" endotracheal cuff. *NY State J Med 71,* 1926.

Nordin, U. & Lyttkens, L. 1976. New self-adjusting cuff for tracheal tubes. *Acta Otolaryngol* (Stockh) *82,* 455.

Nordin, U & Lyttkens, L. Modified parachute cuff and PEEP to minimize tracheal injury and prevent aspiration. (Manuscript.)

Paegle, R.D. & & Bernhard, W.N. 1975. Squamous metaplasia of tracheal epithelium associated with high-volume, low pressure airway cuffs. *Anesth Analg (Cleve) Vol. 54,* No 3, p. 340.

Revenäs, B. & Lindholm, C.-E. 1976. Pressure and volume changes in tracheal tube cuffs during anaesthesia. *Acta Anaesthesiol Scand 20,* 321.

Safar, P., Berman, B., Diamond, E., Hoffman, K., Holtey, W., Moore, H. & Scoville, B. 1962. Cuffed tracheostomy tube versus tank respirator for prolonged artificial ventilation. *Arch Phys Med Rehabil 43,* 487.

Sanders, R.D. 1947. New endotracheal instruments. *Anesthesiology 8,* 57.

Sobin, S.S., Frasher, W.G. Jr., Tremer, H.M. & Hadley, G.G. 1963. The microcirculation of the tracheal mucosa. *Angiology 14,* 165.

Stanley, T.H., Kawamura, R. & Graves, O. 1974. Effects of nitrous oxide on volume and pressure of endotracheal tube cuffs. *Anesthesiology 41,* 256.

Stanley, T.H. 1975. Nitrous oxide and pressures and volumes of high and low-pressure endotracheal-tube cuffs in intubated patients. *Anesthesiology 42,* 637.

Trendelenburg 1871. Beiträge zu den Operationen an den Luftwegen. *Archiv f klin Chir 12,* 112.

Wiederhielm, C.A., Woodbury, J.W., Kirk, S. & Rushmer, R.F. 1964. Pulsatile pressures in the microcirculation of frog's mesentery. *Am J Physiol 207,* 173.

Wilms 1904. Zur Technik der Operationen im Thorax mit Überdruck. *Zentralbl Chir 20,* 633.

Surface structure and vascular anatomy of the tracheal wall under normal conditions and after intubation

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Abstract: The effect of a large tracheal tube cuff on the rabbit tracheal mucosa was investigated by phase contrast microscopy and scanning (SEM) and transmission (TEM) electron microscopy. The tube was left in the trachea for 15 min. The cuff was either uninflated or inflated to a cuff-to-tracheal wall pressure (C-T pressure) of up to 100 mmHg.

The uninflated cuff caused superficial damage to the epithelial lamina over regions where a cartilage was situated.

When the cuff was inflated, it resulted in an increase of the mucosal damage, the extent of which was directly related to the pressure in the cuff. This took the form of both widening of the injured areas and penetration of the damage to deeper regions. At a C-T pressure of 100 mmHg the damage involved almost the entire mucosa and only small unaffected mucosal regions remained. At this stage it appeared as if the basement membrane had also begun to disintegrate.

It is well known that a *small* cuff easily causes deep ulceration in the mucosa overlying the cartilages.

From this investigation it was concluded that a *large* cuff causes the same type of ulceration if 1) the cuff wall is not sufficiently thin and pliable, and 2) if the cuff is overinflated enough to dilate the trachea to a diameter exceeding the cuff-diameter. At that moment there will be circumferential tension in the cuff and the sealing physics of the large cuff will become the sealing physics of a small (high pressure) cuff.

A large cuff, properly handled, is more benign to the trachea than a small cuff. In order to avoid overinflation of the large cuff, the intracuff pressure (= C-T pressure) should always be measured by means of a four-way stopcock and an aneroid manometer. In the case of extended periods of mechanical ventilation with a high airway pressure, the resulting tracheal diameter at the cuff site should be checked radiographically.

Introduction

Tracheal intubation is widely used in anesthesiology. The rapid progress of intensive care during the last decade has made the use of cuffed tubes increasingly common. In many cases the tube is left in situ for long periods. Since many tubes and cuffs exert harmful pressure on the tracheal wall, prolonged intubation sometimes causes sufficient damage to result in a tracheal or laryngeal stenosis. Consequently, the interest in the causative factors underlying tracheal stenosis has increased considerably all over the world. Incidences of tracheal stenosis varying from 1.5 to 20 % have been reported (Pearson et al., 1968; Lindholm, 1969; Grillo, 1970). Investigations by Geffin & Pontoppidan (1969) indicate that the stenosis is most often found in the region where the cuff has exerted its main pressure against the tracheal mucosa. The most widely used cuffs have been of the small-resting-diameter, small-resting-volume type, in the following called *small* cuffs. Many publications have described the damage caused by this type of cuff and most authors have come to the conclusion that the main etiological factor is the high pressure exerted on the tracheal wall (Pearson et al., 1968; Cooper & Grillo, 1969; Shelly et al., 1969; Donnelly, 1969; Hedden et al., 1969; Grillo et al., 1971; Andrews & Pearson, 1971; Hilding, 1971; Magovern et al., 1972; Goldenberg & Pearson, 1972).

It was against this background that many anesthesiologists strove to find better systems for tracheal "seals", and Safar et al. (1962) established that large Sanders cuffs did not produce tracheal damage visible at tracheoscopy. They had used these cuffs in humans over extended periods, but they were unaware of the reasons for these good results. Clinical experience of a similar nature was reported by Lomholt (1967). Other authors (Carroll et al., 1969; Carroll, 1973) found in animal experiments that the design of the cuffs was of primary importance in determining the damage caused and that large-resting-diameter, large-residual-volume cuffs—called in the following *large* cuffs—were able to seal the trachea at a much lower cuff-to-tracheal wall pressure (C-T pressure) than the small ones. Similar findings were made by other authors (Geffin & Pontoppidan, 1969; Cooper & Grillo, 1969 and 1973; Ching et al., 1974).

The evidence from these pioneer investigations enhanced the interest in the design and construction of tubes and cuffs, and experience from human intubations (Ching et al., 1971 and 1974; Grillo et al., 1971; Mathias & Wedley, 1974; Paegle & Bernhard, 1975) and animal experiments (Cooper & Grillo, 1969; Magovern et al., 1972; Ching et al., 1974; Dunn et al., 1974; Klainer et al., 1975) has been reported by many authors.

Some of these publications are of special interest with regard to the studies described in this paper. Grillo et al. (1969) reported on 8 dogs intubated from 5 to 14 days with large cuffs inflated to a constant pressure of 20—40 mmHg. In one dog there was slight discoloration of the mucosa after 13 days, while the rest showed no macroscopic mucosal damage. At light microscopy only mild inflammatory changes were seen.

Magovern et al. (1972) reported on dogs intubated for 3—30 days with a large cuff, where the cuff pressure was controlled and kept around 20 mmHg. No macroscopic damage was seen. After

30 days of intubation light microscopy revealed a well preserved mucosa with flattened epithelium. They also reported on 3 patients in whom the cuff was inflated to 20 mmHg for 45, 55 and 200 days respectively. Endoscopic examination showed no evidence of mucosal damage.

Dunn et al. (1974) described observations on 8 dogs in which large cuffs were inflated to seal (0—10 mmHg) for 10 days. After 5 days 6 of the dogs were subjected to a 12-h period of hypotension (systolic blood pressure 40—60 mm Hg). Three other dogs were on positive pressure ventilation for 96 h. In 10 of these 11 dogs only microscopic hemorrhage was observed at the cuff site, with no mucosal damage. In one dog there were gross mucosal hemorrhages and microscopic erosions at the cuff site. The period of hypotension did not influence the extent of tracheal damage and this is in accordance with the findings of Shelly et al. (1969) and of Mathias & Wedley (1974).

Paegle & Bernhard (1975) reported on 12 patients intubated from 2 h to 20 days with a large-cuffed tube, where the cuff pressure was kept between 20 and 25 mmHg. The cuffs usually did not even erode the entire thickness of the tracheal epithelium. After more than a week of intubation preserved ciliated cells could be found in the intercartilaginous regions.

Klainer et al. (1975) reported on scanning electron microscopic studies of cuff-induced damage. They intubated dogs with large cuffs for a period of 2 h. In dogs in which the cuff was left uninflated, transverse areas with loss of cilia were seen. At a C-T pressure of 18—25 mmHg they also found a diffuse area of ciliary denudation at the cuff site. Light microscopy of the same areas revealed almost complete destruction of the mucosa, however.

When we started the present investigation, all previous studies in animals and clinical investigations had employed tracheoscopy and histopathologic examination with light microscopy for evaluation of the damage.

Tracheal damage caused by intubation continued, however, to be a problem needing further investigation. With the development of improved methods for structural research it was therefore considered of value to apply such techniques as improved light microscopy and scanning and transmission electron microscopy.

Several convincing reports have already demonstrated a reduction in cuff site tracheal injury with large cuffs, as compared with small ones (Cooper & Grillo, 1969; Grillo et al., 1971; Ching et al., 1971; Dunn et al., 1974; Mathias & Wedley, 1974; Paegle & Bernhard, 1975). In the present study, therefore, we focused our interest on the effect of the *large* cuff, rather than on comparison with that of the small cuff.

The aim of this investigation was to study

1) the normal tracheal mucosa,

2) the damage to the tracheal mucosa caused by intubation for a constant length of time with a tube equipped with a large cuff, inflated to different C-T pressures,

3) the vascular anatomy of the tracheal mucosa by arterial infusion of silicone rubber and the effect of an inflated large cuff on the vascular bed. (For further details see Nordin & Lindholm, 1977 a).

In parallel we have studied

1) the effect on the mucosa of different durations of intubation, keeping the C-T pressure constant (Nordin et al., 1977 b),

2) the capillary blood perfusion pressure and fluid dynamics of the tracheal mucosa, by the micropuncture technique (Nordin et al., 1977 c),

3) the effect of different C-T pressures on the capillary blood flow of the tracheal mucosa (Nordin et al., 1977 d).

Material and methods

Fifteen white rabbits, weighing 2–2.5 kg, were used. Three of them were used for a study of the normal morphology of the mucosa, 2 for a study of the normal vascular bed and 10 for a study of the effect of intubation. To ascertain whether the rabbit was as suitable as the cat for studies of the tracheal blood perfusion, one adult cat was used to visualize the vascular bed.

The structure of the tracheal wall was examined by direct observation—using a binocular preparation microscope (Wild M 5), and by phase contrast microscopy and by scanning (SEM) and transmission (TEM) electron microscopy. The techniques for SEM and TEM were those currently used in our clinic (Ades & Engström, 1972). For SEM the specimens were fixed in buffered 2.5 % glutaraldehyde, dehydrated in 70 % ethanol and 70 % acetone and stored in pure acetone for at least two days before being dried by the critical point technique (Andersson, 1951). After being coated with gold in a "sputter", the specimens were examined in a JSM-U 3 microscope.

The vascular anatomy was studied after injection of silicone rubber (Canton Bio-Medical Products Inc., Box 2017, Boulder, Colorado 80302, USA) into the blood vessels (Nordin & Lindholm, 1977 a). After micro-dissection and dehydration the specimens were immersed in glycerol or methyl-salicylate, which rendered them transparent and permitted excellent visualization of the blood vessels of the tracheal wall.

For light microscopy and TEM two methods were used. With the first technique the specimens were fixed in buffered 2.5 % glutaraldehyde, post-fixed in 1.5 % osmium tetroxide for 1.5 h and embedded in Epon 812 (Luft, 1961). With the second technique the specimens used for SEM were immersed for 24 h in propylene oxide and embedded in Epon 812. The specimens for light microscopy and TEM were sectioned in an LKB Ultrotome. The TEM specimens were studied in a Siemens Elmiskop IA.

Intubation, tube and cuff. The rabbits were anesthetized by an intravenous injection of 2 % sodium pentobarbital (Nembutal®) in a dose of 50–60 mg/kg body weight. They breathed spontaneously throughout the experiment. A specially made PVC tube (Portex) with an inner diameter (ID) of 2.5 mm and an outer diameter (OD) of 3.5 mm, equipped with a large cuff, was placed in the trachea by translaryngeal intubation. The thickness of the cuff wall varied slightly around 0.10 mm depending upon the degree of prestreching (Geffin & Pontoppidan, 1969). When the cuff was deflated the diameter of the tube and cuff varied between 4.2 and 3.9 mm, depending upon the folds in the cuff. The length of the cuff was approximately 15 mm. The diameter of the trachea was about 5 mm.

The tube, with the cuff deflated, was placed in the cervical portion of the trachea, well below the larynx, and left in place for 15 min either uninflated or inflated to different cuff pressures as measured according to Cox & Schatz (1974). By measuring the pressure in a cuff with large-diameter, high-volume characteristics the C-T pressure is also known, as they are identical so long as there is no circumferential tension in the cuff wall (Carroll et al., 1974). The animals were killed directly after this procedure by injection of Nembutal® and air.

Results

The normal tracheal wall

The normal tracheal wall was found to consist of a mucus membrane and a series of horse-shoe shaped cartilages of the same appearance as in the human trachea. The surface layer of the mucosa is built up of a *pseudostratified columnar ciliated epithelium* containing many goblet cells. This rests on a rather thick (1000 Å) basement membrane, beneath which is a loose network of connective tissue cells and fibers forming the lamina propria. In this layer there is a rich capillary network.

The submucosal layer also contains loose connective tissue and rather large groups of tubulo-alveolar sero-mucus glands. These glands and the goblet cells together produce the mucus coating the tracheal wall. The ciliated cells are very numerous and cover a large part of the tracheal surface. In scanning electron micrographs large areas of tracheal mucosa may be surveyed (Fig. 1) and it is also fairly easy to differentiate between ciliated and goblet cells. The combined use of SEM and TEM (Fig. 2) gives excellent information on the structure of the tracheal mucosa. Each ciliated cell extends from the basement membrane to the epithelial surface. These cells have an ovoid nucleus located in their lower half, and contain an endoplasmic reticulum, a large number of mitochondria and other cytoplasmic organelles. The free upper surface of the cells is provided with large numbers of cilia, the number varying with the area of the free surface. Between the cilia there are numerous microvilli. The cilia are 6—7 μm long and approximately 0.2 μm in diameter. They taper slightly at the distal end, and have an axial filament complex and a surrounding matrix. The outer membrane of the cilium is continuous with the plasma membrane of the cell. The axial filament complex generally consists of 11 internal fibrils arranged with two in the center and nine surrounding evenly spaced double fibrils (Fig. 3). As will be shown in this paper cilia with a deviating arrangement in the axial filament complex are often found, especially in tracheal mucosa affected by different forms of lesions. Also in "normal" tracheae cilia with quite differing internal structures may be seen, as well as some giant cilia. Giant cilia seem to be more numerous in damaged cells (Fig. 7 b).

Towards the tip of the cilium the nine peripheral double fibrils become single and a reduction in number is often evident. Each cilium has a basal body and a tapering, cross-striated rootlet at the cell surface. The rootlet can be followed far down into the cell.

The goblet cells or mucus producing cells are quite different in appearance from the ciliated cells, being goblet-shaped with an upper widened portion and a slender foot. The nucleus is located in the lower part of the cell. There is a well developed Golgi complex close to the nucleus. It is assumed that secretory granules are formed in this region and that these fill the upper goblet-shaped or thecal portion of the cells. At TEM and light microscopy these granules are round, rather large and densely packed. The cytoplasm contains many ribosomes, and also often numerous lysosomes. The free surface of the cells is often richly provided with microvilli. The cytoplasm contains numerous mitochondria and at the basal end a rough endoplasmic reticulum.

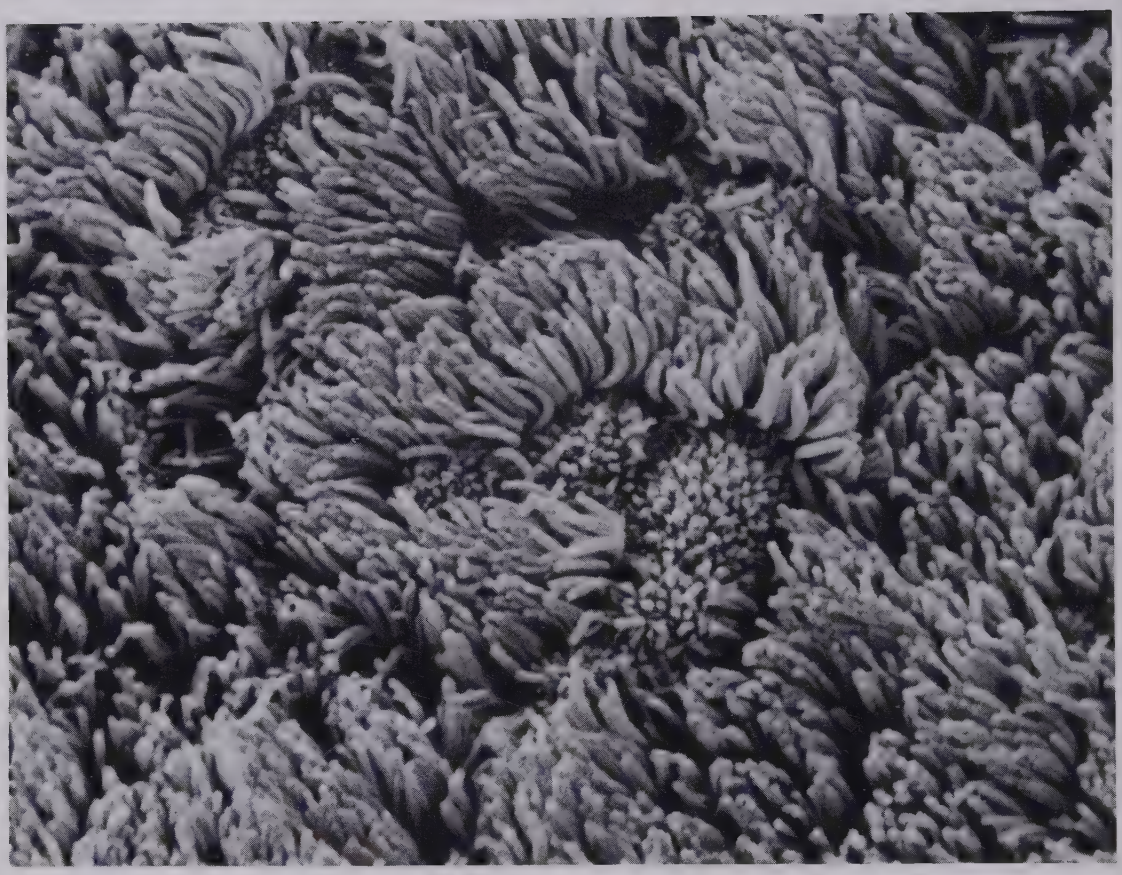

Fig. 1. Scanning electron micrograph of the normal tracheal epithelium of the rabbit, with many ciliated and a few non-ciliated cells with microvilli. ×5 100.

The tracheal wall after intubation

Generally the major damage to the tracheal wall after intubation is caused by the cuff, though minor injury may be caused by the endotracheal tube. In the following we shall only deal with damage caused by the cuff. The intubation time was kept constant at 15 min.

When the tube was placed in the trachea without inflation of the cuff it was quite clear that this was sufficient to cause minor superficial damage to the epithelial lamina. At SEM it was evident that this damage only occurred over regions where a cartilage was situated. In the intercartilaginous regions no damage was seen (Fig. 4). In the injured regions TEM revealed that the ciliated cells had largely lost their cilia; the basal bodies were sometimes present, however, and close to the surface the cytoplasm was vacuolated.

In this series the damage was found not to have penetrated the basement membrane. The normal tracheal epithelium has been described above as rather high and pseudostratified. Close to areas of damage we repeatedly found regions still retaining cilia with a fairly normal appearance but the thickness of the epithelium had become reduced. In these regions two layers or a single layer of ciliated cells were seen. How this modification develops is not clear, but it may be assumed that the pressure in some way promotes a lateral movement of the cells towards the center of maximal damage (Fig. 5). Another feature was that in regions of incipient damage microvilli between the kinocilia had started to disappear.

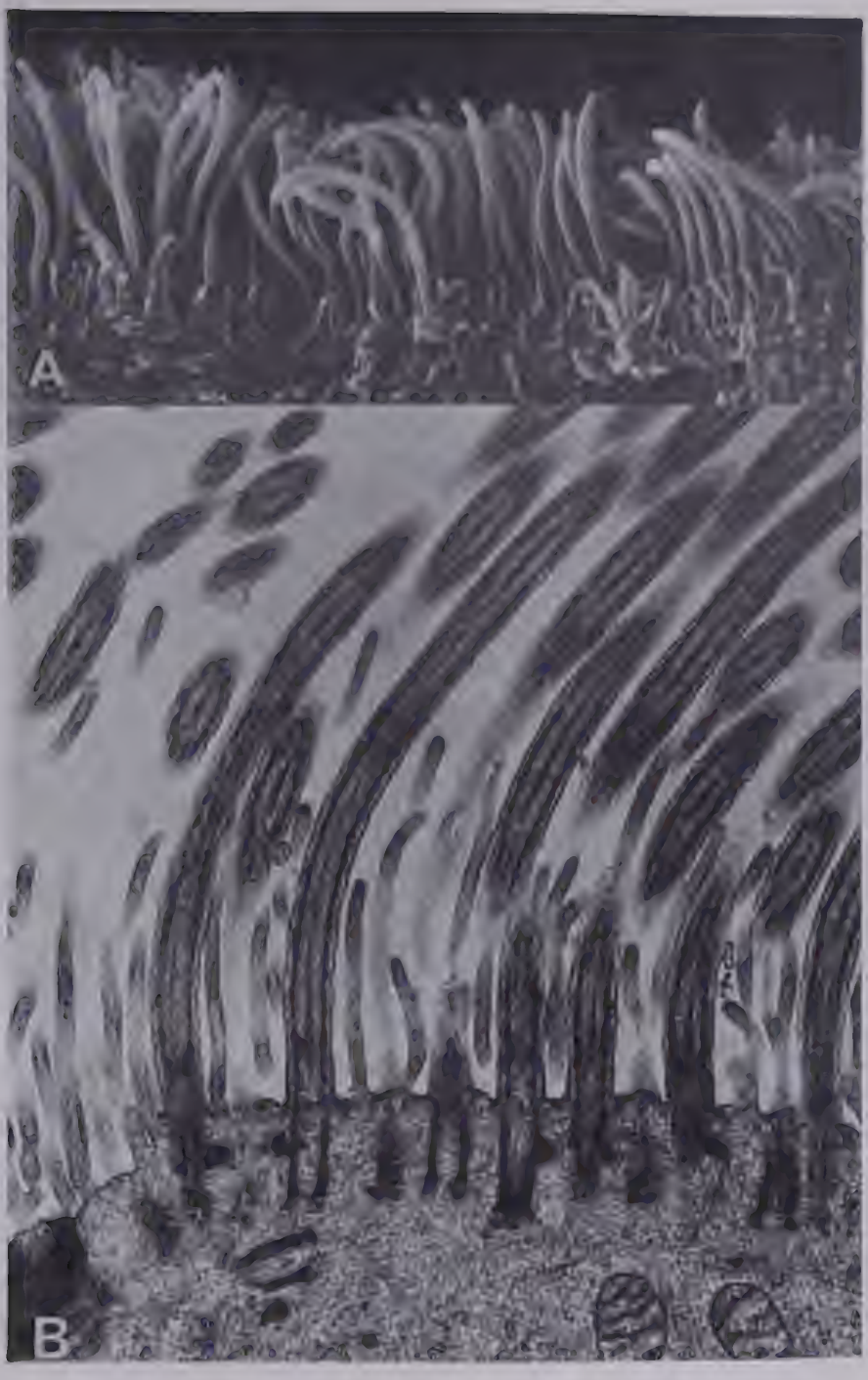

Fig. 2a. Scanning electron micrograph of normal tracheal mucosa from the rabbit. The tracheal cilia and the interciliary microvilli are clearly seen. ×7 300.
Fig. 2b. Transmission electron micrograph from the same part of the mucosa as in *a*. ×34 500.

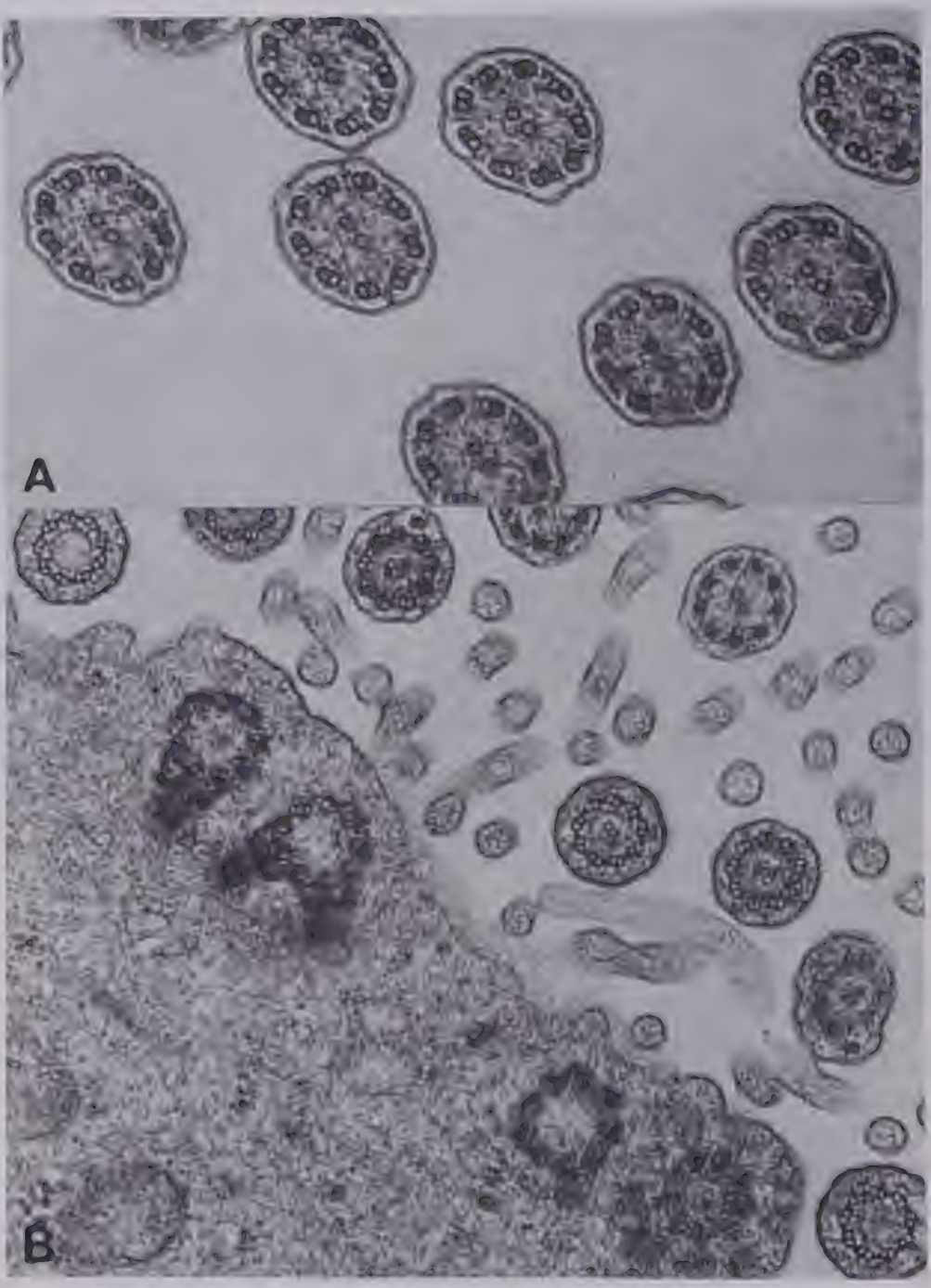

Fig. 3a. Cross-sectioned tracheal cilia. In each cilium nine double fibrils are surrounding two central single fibrils. × 126 000.

Fig. 3b. Cilia close to and below the cell surface. A comparison between *a* and *b* shows that the cilia change their structure when entering the cell surface. Both from normal rabbit mucosa. × 92 000.

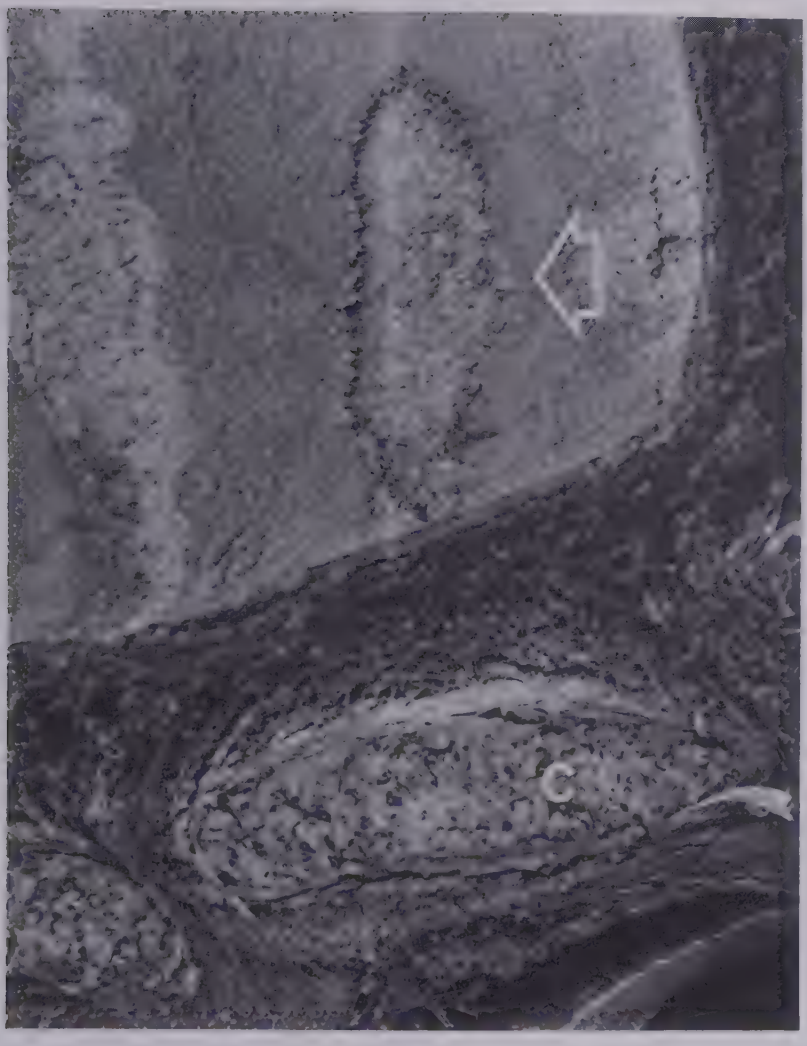

Fig. 4. Minor mucosal damage to a rabbit trachea after 15 min of intubation but without inflation of the cuff. Superficial damage *(arrow)* can be seen over the tracheal cartilage (C). ×70.

Inflation of the cuff resulted in an increase of the mucosal damage, the extent of the injury being directly related to the pressure in the cuff. A gradual increase in C-T pressure thus led to progressive extension of the mucosal damage. This took the form of both widening of the injured areas and penetration of the damage to deeper regions. Often complete denudation, but no penetration, of the basement membrane was seen, with only some scattered cells remaining. Regions with almost no epithelial cells, lying close to regions with almost normal epithelium, were commonly found. Fig. 6 shows how *C-T pressures of 20 or 30 mmHg* caused fairly deep injuries but no penetration of the basement membrane. In the center of the damaged area in Fig. 6 b the ulceration reached the basement membrane and almost all cells were lost. Close to this more severely damaged area partly disintegrated cells and cells with cytoplasmic vacuolization and partly destroyed cilia were seen (Fig. 7 b).

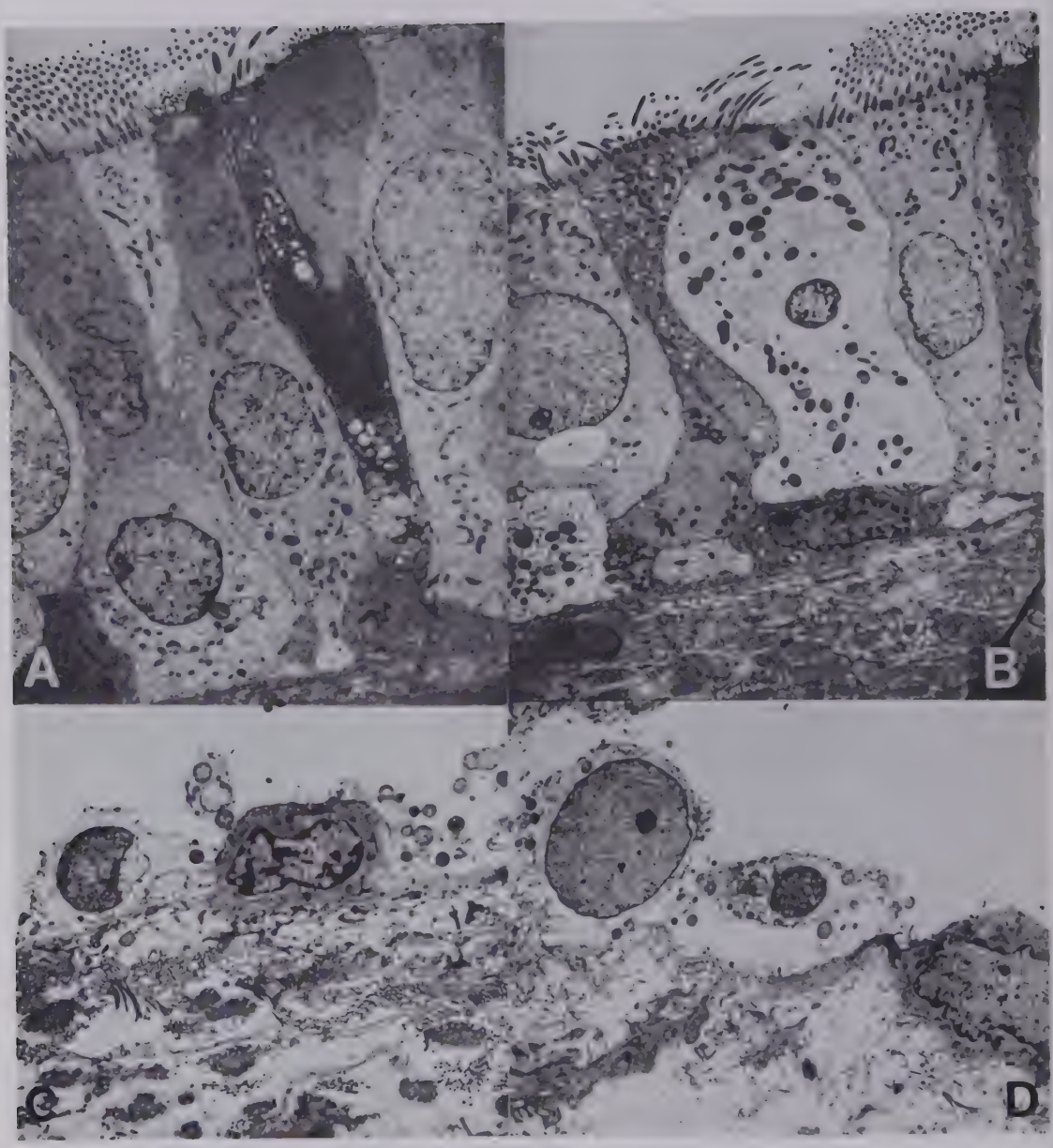

Fig. 5. In these four transmission electron micrographs from rabbit tracheae exposed to a C-T pressure of 100 mmHg for 15 min, it is seen how fairly adjacent regions contain cells differing greatly in appearance. Some cells *(a)* are only slightly modified, others are forming a low epithelium *(b)* and a third group *(c, d)* are forming only scattered, degenerating cells at the basement membrane. *(a)* ×3 100. *(b)* ×3 100. *(c)* ×3 200. *(d)* ×3 300.

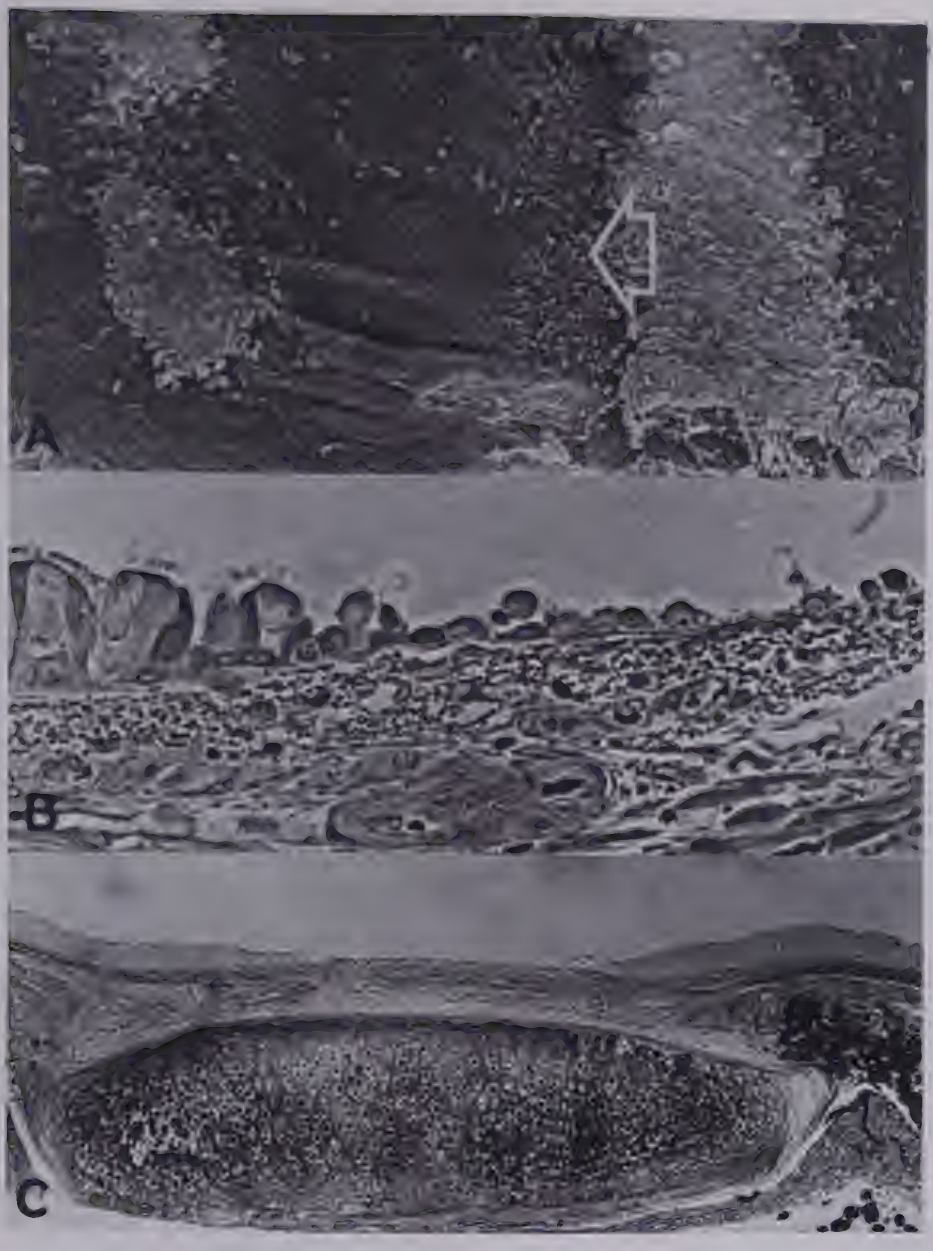

Fig. 6. Rabbit tracheal mucosa exposed to a C-T pressure of 20 mmHg for 15 min, showing incipient degeneration over the cartilages. In *a* a scanning electron micrograph shows the dark areas of degeneration *(arrow).* In *b,* phase contrast microscopy reveals the destruction of the epithelium in a damaged area. In *c* a corresponding area at low magnification is seen. The damage over the tracheal cartilage is very clear. *(a)* ×180. *(b)* ×600. *(c)* ×50.

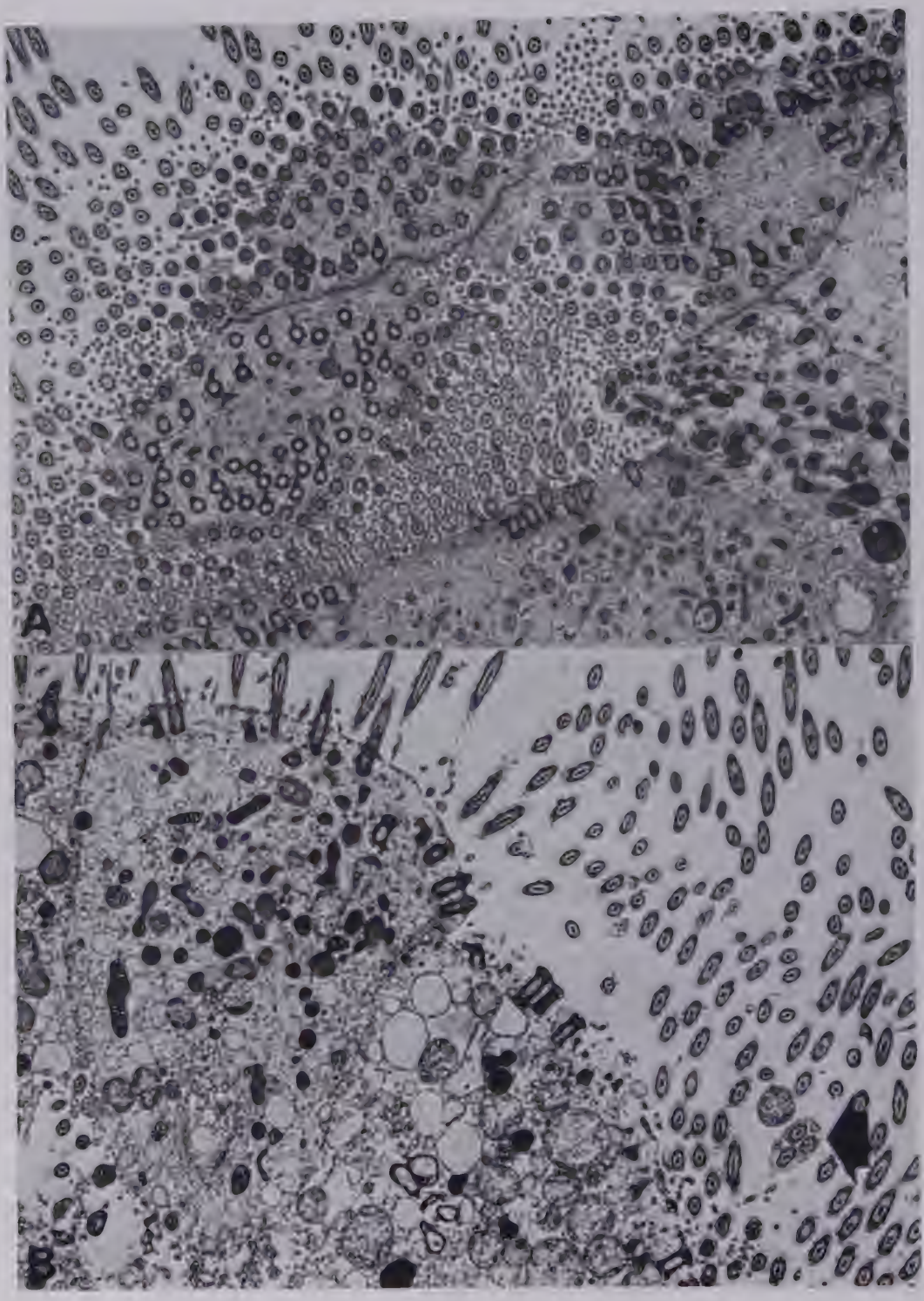

Fig. 7. Transmission electron micrographs from two adjacent regions of a rabbit trachea exposed to a C-T pressure of 30 mmHg for 15 min. In *a* the cells and the cilia are well preserved. ×8 900. In *b* the cells seem to be degenerating. One triple cilium can be seen *(arrow)*, possibly a result of fusion. ×9 100.

Fig. 8. Scanning electron micrographs showing rather deep damage *(arrow)* to the tracheal epithelium from a rabbit exposed to a C-T pressure of 50 mmHg for 15 min. In *b* it can be seen how the basement membrane is almost devoid of epithelial cells. *(a)* ×70. *(b)* ×450.

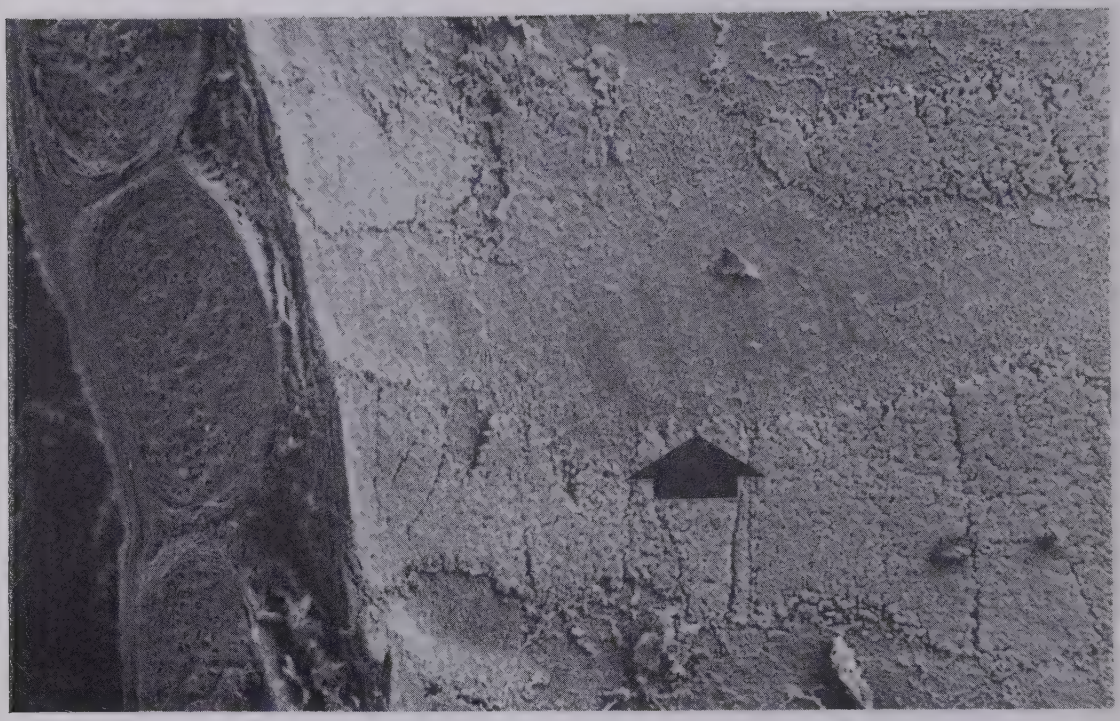

Fig. 9. Further extension of the mucosal damage *(arrow)* in a rabbit trachea exposed to a C-T pressure of 80 mmHg for 15 min. The damage is most pronounced over the cartilages. ×80.

Fig. 7 a shows that only a few cells away from where Fig. 7 b was taken, well ciliated cells were present. It seemed as if the cells were able to withstand a certain pressure but when the surface structures became damaged the cells rapidly disintegrated. The impact of infection could not be evaluated, but as the intubation time was only 15 min infection could not have progressed very deeply. Some lympholeucocytic reaction was observed, however, even at this stage (Fig. 7 b).

With an increase of the *C-T pressure to 50–60 mmHg* the damage was slightly greater but the injured areas were found mainly over the cartilages, while the epithelium in the regions between them seemed to be hardly affected (Fig. 8 a). In the scanning electron micrographs in Fig. 8 b it can be seen how the injured regions were almost devoid of cells and the basement membrane was practically denuded. The intercartilaginous regions, however, and the membranous portion of the tracheal wall retained a fairly normal appearance. When the *C-T pressure exceeded 80 mmHg* the major damage was still found over the cartilaginous portions but now the injuries were more extensive, widening irregularly and invading intercartilaginous regions (Fig. 9). At a *C-T pressure of 100 mmHg* the damage afflicted almost the entire mucosa and only small undamaged mucosal regions remained. At this stage it appeared as if the basement membrane had also begun to disintegrate (Fig. 10).

The vascular bed of the tracheal wall

The vascular bed of the tracheal wall has been described by Nordin & Lindholm (1977 a). The main principles of the vascular organization are illustrated in Fig. 11. The effect of an inflated large cuff on the vascular bed is shown in Fig. 12.

Fig. 10. In *a,* a scanning electron micrograph shows extensive damage *(arrows)* to a rabbit trachea exposed to a C-T pressure of 100 mmHg for 15 min. ×60. In *b* and *c* more or less complete denudation of the basement membrane is seen. There also seems to be some disintegration of the basement membrane *(b). (b)* ×900. *(c)* ×900.

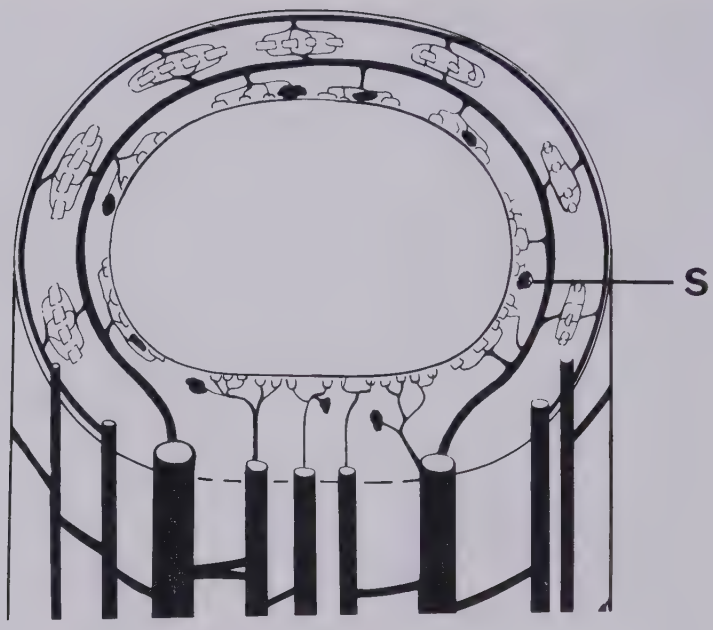

Fig. 11. Schematic drawing showing the vascular anatomy of the rabbit tracheal wall. S = sinusoids or cavernous vascular spaces in the submucosa.

Fig. 12. Cat tracheal mucosa with silicone rubber infused into the vessels. The cuff was inflated during the infusion. The arrow shows the borderline between the cuffed part of the mucosa with no silicone rubber in the vessels (to the left), and the uncuffed part with vessels filled with silicone rubber (to the right). At the cuffed area the mucosal vessels are obviously being occluded by pressure from the inflated cuff.

Discussion

The fine structure of the tracheal epithelium has been extensively studied by several authors, both by TEM (Rhodin, 1966; Konrádová, 1966; Mecklenburg et al., 1974) and by SEM (Barber & Boyde, 1968; Holma, 1969; Dalgren et al., 1972; Mecklenburg et al., 1974).

Rhodin (1966) distinguished at least three different cell types in the tracheal epithelium. At the basement membrane basal cells with a rather large nucleus form an irregular layer and ciliated cells and goblet cells form the upper portion of the epithelial lamina. The ciliated cells predominate. Many authors have distinguished a further group of intermediate cells, which reach from the basement membrane to the upper half of the epithelial layer. For the present study the ciliated cells were of special interest as they are the structures in immediate contact with the endotracheal tube. Rhodin (1966) estimated the number of cilia per cell at about 200 but we have seen cells with more than 1000 cilia and also cells with fewer than 200. Even in "normal" tracheal epithelium cilia with quite differing internal structures may be seen, as well as some giant cilia. Giant cilia (Fig. 7 b) are more numerous in damaged areas.

The reaction of the subepithelial tissues to intubation is also of great importance. This is especially true for the vascular bed and the hyaline tracheal cartilages. These cartilages with their well developed perichondrium form elastic horse-shoe shaped reinforcements in the tracheal wall and their function is of mandatory importance, to prevent the trachea from collapsing.

Numerous studies have been reported concerning the damage caused by intubation but in many of them the small high-pressure cuff has been employed. In such an experimental set up the C-T pressure is extremely difficult to ascertain. Clear evidence has now been produced that large cuffs are less injurious.

In our studies the cuffs were prestretched (Geffin & Pontoppidan, 1969) to obtain large-resting-diameter, large-residual-volume cuff properties (Lomholt, 1967; Carroll & Grenvik, 1973; Carroll et al., 1974) in relation to the rabbit trachea. The cuff wall, however, proved to be not sufficiently thin and pliable to possess the properties of an *ideal* large cuff. The ideal large cuff should drape freely over the mucosa, allowing the C-T pressure to be distributed evenly over this surface, including the mucosa covering the intercartilaginous regions.

Our results have been influenced by the fact that the wall of the cuff was rather thick in relation to the thickness of the rabbit tracheal mucosa. This fact should be borne in mind when interpreting the results. Although the resting diameter and residual volume were large enough for it to be classified as a large cuff, the pressure dynamics against the rabbit tracheal wall resembled at least partly those of a small cuff, due to the rigidity and relative thickness of the cuff wall.

It is quite clear from our experiments that even an uninflated cuff of an endotracheal tube damages the surface of the tracheal mucosa. This could be expected from the early experiments by Hilding (1952), and this question was further discussed in his more recent studies (1971). Our observation is also in accordance with the findings of Klainer et al. (1975). The shearing forces of the cuff at intubation and extubation probably contribute to the lesions even if the cuff is completely

deflated during these procedures and great care is taken to avoid surface damage to the airway. It is also quite clear that if the period of intubation had been longer than 15 min, or if there had been significant movement of the rabbit's head, then the shearing forces may have become a more significant factor.

In the present experiments some areas, especially on the mucosa covering the tracheal cartilages, lost their cilia and in small areas ciliated cells also disappeared.These lesions were rather scattered, however, and did not cover large confluent areas. From a functional point of view this might mean that the capacity for mucus transport along the trachea is reduced but not completely eliminated.

From analyses of tube deformation forces (Lindholm, 1969; Lindholm & Carroll, 1975) exerted on the airway by a tube of conventional shape, it is evident that on intubation and extubation the tip of the tube is likely to scratch the anterior tracheal mucosa and the force applied posteriorly may also play a certain role. This was also emphasized by Hilding (1971). Such lesions may occasionally interfere with the interpretation of cuff damage but in this analysis we have little reason to believe that this is the case.

We are convinced that when it is reported that no or only minor damage to the tracheal mucosa has been found at investigations similar to the present one, the explanation is that SEM has not been used. This method permits detailed observation of large areas of the mucosa and allows selection of the most severely damaged areas for light microscopy and TEM, which will give further information on the ultrastructure of the specific lesions. Such lesions may otherwise be overlooked.

It is also evident from the present study that the C-T pressure is of major significance for the extent and depth of the damage caused by the cuff. As stated above, however, even an uninflated cuff causes a certain amount of damage, but our experiments also clearly demonstrate that C-T pressure and the magnitude of damage are directly related. At ordinary C-T pressures of 15—20 mmHg for 15 min the surface lesions may not differ greatly from those caused by shearing forces of a deflated cuff at intubation. At higher C-T pressures the epithelial lesions become deeper and more confluent. The majority of the epithelial cells at the cuff site are thus destroyed at C-T pressures of 80—100 mmHg or more. At this stage it appeared as if the basement membrane had also begun to disintegrate. In this connection it is to be noted that all small slip-on tracheostomy cuffs tested by Carroll et al. (1969) exerted a C-T pressure of 130—147 mmHg for minimum no-leak ventilation.

In addition to C-T pressure the time factor is of importance in the development of tracheal wall damage. This has been further elucidated in another study (Nordin et al., 1977 b), which is also reported in this supplement.

We have just described how in our experiments the surface epithelium disappeared in some areas, but in others was only compressed. After a short intubation period the basement membrane was, however, usually retained. This membrane constitutes an important protective layer against severe damage. In some of our animals it was slightly disintegrated. In such cases an invasion of lympholeucocytic cells close to the membrane and even into the remaining epithelial border regions was sometimes seen.

It was also quite clear that the damage began and was most pronounced at the mucosa covering the tracheal cartilages. This is explained by the fact that the wall of the cuff used was not sufficiently thin and pliable to have the properties of an ideal large cuff, in relation to the smallness of the rabbit trachea. The ideal large cuff should drape quite freely over the mucosa, allowing the C-T pressure to be distributed evenly, i.e. also, to a certain degree, to the intercartilaginous areas. Our cuffs did not quite possess this property, as they often left this part of the mucosa untouched, even when inflated to fairly high C-T pressures. This emphasizes the importance of the quality of the cuff wall. The thicker and the more rigid it is, the more will the cuff act as a small-volume type, i.e. it will ride on the edges of the cartilages. This will increase the risk of local ulceration, which may penetrate the basement membrane at the mucosa covering the cartilages and eventually threaten the cartilages themselves. In contrast, commercially

available, extremely thin-walled large cuffs, used in 72 h intubation tests on dogs, have seemed to be in contact with the entire mucosa at the cuff site, even when inflated to only 15 mm Hg (Lindholm et al., 1977). This means that there are some thin-walled large cuffs available today that more closely approach the ideal cuff than the cuff used in our experiments.

The thinner the cuff wall and the more pliable the cuff wall relative to the tracheal mucosa, the greater is the surface area upon which the sealing force is distributed. This explains the higher frequency of sore throats after the use of large cuffs than with small cuffs, reported by Loeser et al. (1976). Their study demonstrates that when extremely high C-T pressures, as a result of nitrous oxide-oxygen anesthesia, are exerted over the tracheal mucosa for roughly 3 h of standard anesthetic time, more sore throats are found with large cuffs than when small cuffs are used. In the latter case the area of tracheal damage is, of course, smaller.

The results of our studies of the effect of C-T pressure on the blood perfusion of the mucosa in contact with the cuff used (Nordin et al. 1977 d) revealed that some blood perfusion was still taking place even when the calculated perfusion pressure was zero or even negative, suggesting that the cuff had not transmitted the entire C-T pressure to all parts of the mucosa at "cuff level" and thus allowed the blood perfusion to persist in some intercartilaginous spaces. It is concluded that if the wall of a large cuff is very thin and pliable the blood circulation in the mucosa may continue, at least for some time, even at C-T pressures exceeding 30 mmHg (approximate capillary perfusion pressure in the tracheal mucosa). The same study also indicated that a non-ideal cuff probably stops the circulation in the mucosa covering the cartilages at C-T pressures exceeding 30 mmHg.

A large cuff with a thin and pliable wall will distribute the cuff pressure over a large area of tracheal mucosa and will seal at a low C-T pressure. It must be emphasized, however, that the use of large cuffs at high pressures allows the high intracuff pressure to be transmitted undiminished until such time as the diameter of the trachea exceeds the diameter of the cuff, and thus circumferential tension within the cuff starts to limit the effective C-T pressure. At such a time, the trachea is already dilated, and the physics of seal become the physics of small cuff (high pressure) sealing, which were elaborated by Carroll et al. (1974).

In order to avoid overinflation of the large cuff, the intracuff pressure (= C-T pressure) should always be measured by means of a four-way stopcock and an aneroid manometer. In the case of extended periods of mechanical ventilation with high airway pressure, the resulting tracheal diameter at the cuff site should be checked radiographically.

Conclusions

1. Any tracheal intubation will produce surface lesions of the mucosa.

2. The degree of damage is directly related to the C-T pressure.

3. In this study C-T pressures of 20–30 mmHg sometimes produced small areas of lesions penetrating the epithelial layer after 15 min of intubation.

4. C-T pressures above 50 mmHg often produced widespread areas of destroyed epithelium, leaving the basement membrane visible.

5. The basement membrane, on the other hand, seemed to constitute a good protection against deeper penetration of the lesion, not being disintegrated until C-T pressures of about 100 mmHg for 15 min.

6. A thick-walled large cuff tends to give lesions similar to those seen after the use of a small cuff.

Acknowledgements

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Zusammenfassung

Die Wirkung einer grossen Schlauchmanschette auf die Schleimhaut der Kaninchenluftröhre wurde mit sowohl Fasenkontrastmikroskopie als aus Scanning- (SEM) und Transmissionselektronenmikroskopie (TEM) untersucht. Der Schlauch lag 15 Minuten in der Trachea. Die Manschette war entweder unaufgeblasen oder wurde auf "cuff-to-tracheal wall" Drucke bis zu 100 mm Hg aufgeblasen.

Die unaufgeblasene Manschette verursachte Oberflächenschäden der Epithelschicht in Regionen mit Knorpelunterlage.

War die Manschette aufgeblasen, kam es zu einer vermehrten Schleimhautschädigung, deren Ausmass direkt vom Manschettendruck abhängig war. Sie äusserte sich sowohl in einer Erweiterung des betroffenen Abschnittes als auch in einer Schädigung tieferer Schichten. Bei einem C-T Druck von 100 mm Hg war fast die gesamte Schleimhaut geschädigt. Nur kleine Schleimhautabsnitte blieben unversehrt. In diesem Stadium zeigte auch die Basalmembran Anzeichen beginnenden Zerfalles.

Es ist bekannt, dass eine *kleine* Schlauchmanschette leicht zu tiefgreifenden Ulzerationen der Schleimhaut über dem Knorpel führt.

Aus dieser Untersuchung geht hervor, dass eine *grosse* Schlauchmanschette zu einer ebenartigen Form von Ulzerationen führt, wenn einerseits die Manschettenwandung nicht genügend dünn und geschmeidig ist und wenn andereseits die Manschette derart aufgeblasen wird, dass die Trachea zu einer Weite ausgedehnt wird, die den Durchmesser der Manschette übertrifft. Es kommt gleichzeitig zu einer Peripheriespannung in der Manschette und damit zum gleichen physicalischen Abdichtungseffekt wie bei der kleinen Manschette mit hohem Druck.

Eine grosse, mit entsprechender Sorgfalt eingeführte Schlauchmanschette ist für die Luftröhre schonender als eine kleine Manschette. Um ein übermässiges Aufblasen der Manschette zu vermeiden, sollte der Innendruck der Manschette (= C-T pressure) mit Hilfe eines Anaeroidmanometers über einen Vierweghahn gemessen werden. Wenn über längere Zeit mechanische Ventilation mit hohem Luftwegedruck betrieben wird, sollte der dabei verursachte Durchmesser der Luftröhre mit dem Situs der Schlauchmanschette röntgenologisch kontrolliert werden.

References

Ades, H.W. & Engström, H. 1972. Inner ear studies. *Acta Otolaryngol* (Stockh) *Suppl 301.*

Andersson, T.F. 1951. Technique for the preservation of three-dimensional structure in preparing specimens for the electron microscope. *Trans NY Acad Sci 13,* 130.

Andrews, M.J. & Pearson, F.G. 1971. Incidence and pathogenesis of tracheal injury following cuffed tube tracheostomy with assisted ventilation: analysis of two year prospective study. *Ann Surg 173,* 249.

Barber, V.C. & Boyde, A. 1968. Scanning electron microscopic studies of cilia. *Z Zellforsch Mikrosk Anat 84,* 269.

Carroll, R.G. 1973. Evaluation of tracheal tube cuff designs. *Crit Care Med 1,* 45.

Carroll, R.G. & Grenvik, Å. 1973. Proper use of large diameter, large residual volume cuffs. *Crit Care Med 1,* 153.

Carroll, R.G., Hedden, M. & Safar, P. 1969. Intratracheal cuffs: performance characteristics. *Anesthesiology, Vol. 31,* No 3.

Carroll, R.G., McGinnis, G.E., & Grenvik, Å. 1974. Performance characteristics of tracheal cuffs. *Int Anesthesiol Clin, Vol. 12,* No 3, p. 111.

Ching, N.P., Ayres, S.M., Paegle, R.P., Linden, J.M. & Nealon, T.F. 1971. The contribution of cuff volume and pressure in tracheostomy tube damage. *J Thorac Cardiovasc Surg 62,* 402.

Ching, N.P., Ayres, S.M., Spina, R.C. & Nealon, T.F. 1974. Endotracheal damage during continuous ventilatory support. *Ann Surg Vol. 179,* No 2, p. 123.

Cooper, J.D. & Grillo, H.C. 1969. Experimental production and prevention of injury due to cuffed tracheal tubes. *Surg Gynec Obstet 129,* 1235.

Cooper, J.D. & Grillo H.C. 1969. The evolution of tracheal injury due to ventilatory assistance through cuffed tubes. *Ann Surg 169,* 334.

Cooper, J.D. & Grillo, H.C. 1973. Analysis of problems related to cuffs on intratracheal tubes. *Chest 62,* 215.

Cox, P. & Schatz, E. 1974. Pressure measurements in endotracheal cuffs: a common error. *Chest 65,* 84.

Dahlgren, S.E., Dalen, H. & Dalhamn, T. 1972. Ultrastructural observations on chemically induced inflammation in guinea pig trachea. *Virchows Arch (Zellpathol) 11,* 211.

Donnelly, W.H. 1968. Histopathology of endotracheal intubation. *Arch Path 88,* 511.

Dunn, R.C., Dunn, D.L. & Moser, K.M. 1974. Determinants of tracheal injury by cuffed tracheostomy tubes. *Chest 65,* 128.

Geffin, B. & Pontoppidan, H. 1969. Reduction of tracheal damage by prestretching of inflatable cuffs. *Anesthesiology 31,* 462.

Goldenberg, M. & Pearson, F.G. 1972. Pathogenesis of tracheal stenosis following tracheostomy with a cuffed tube. *Thorax 27,* 678.

Grillo, H.C. 1970. Surgery of the trachea. *Current problems in surgery, p. 3,* Year book medical publishers, Inc., Chicago.

Grillo, H.C., Cooper, J.D., Geffin, B. & Pontoppidan, H. 1971. A low pressure cuff for tracheostomy tubes to minimize tracheal injury—a comparative clinical trial. *J Thorac Cardiovasc Surg 62,* 898.

Hedden, M., Ersoz, C.J. & Safar, P. 1969. Tracheoesophageal fistulas following prolonged artificial ventilation via cuffed tracheostomy tubes. *Anesthesiology 31,* 281.

Hilding, A.C. 1971. Laryngotracheal damage during intratracheal anaesthesia. *Ann Otol 80,* 565.

Hilding, A.C. & Hilding, J.A. 1952. Tolerance of the respiratory mucous membrane to trauma: surgical swabs and intratracheal tubes. *Ann Otol 71,* 455.

Holma, B. 1969. Scanning electron microscopic observation of particles deposited in the lung. *Arch Environ Health 18,* 330.

Klainer, A.S., Turndorf, H., Wu, W-H., Maewal, H. & Allender, P. 1975. Surface alterations due to endotracheal intubation. *Am J Med Vol. 58,* 674.

Konrádová, V. 1966. The ultrastructure of the tracheal epithelium in rabbit. *Folia Morphol (Praha) 14,* 210.

Lindholm, C-E. Prolonged endotracheal intubation. *Acta Anaesthesiol Scand Suppl XXXIII.*

Lindholm, C-E. & Carroll, R.G. 1975. Evaluation of tube deformation pressure in vitro. *Crit Care Med 3,* 196.

Lindholm, C-E., Carroll, R.G. & Nordin, U. 1977. Controlled 72-hour tracheal intubation test in dogs. (In preparation.)

Loeser, E.A., Orr, D.L., Bennett, G.M. & Stanley, T.H. 1976. Endotracheal tube cuff design and postoperative sore throat. *Anesthesiology Vol. 45, No 6,* 684.

Lomholt, N. 1967. A new tracheostomy tube: Cuff with controlled pressure on the tracheal mucous membrane. *Acta Anaesthesiol Scand 11,* 311.

Luft, J.H. 1961. Improvements in epoxy resin embedding methods. *J. Biophys Biochem Cytol. 9,* 409.

Magovern, G.J., Shively, J.G., Fecht, D. & Thevoz, F. 1972. The clinical and experimental evaluation of a controlled-pressure intratracheal cuff. *J Thorac Cardiovasc Surg 64,* 747.

Mathias, D.B. & Wedley, J.R. 1974. The effects of cuffed endotracheal tubes on the tracheal wall. *Br J Anaesth 46,* 849.

Mecklenburg, C.v., Mercke, K., Håkansson, C.H. & Toremalm, N.G. 1974. Morphological changes in ciliary cells due to heat exposure. *Cell Tiss Res 148,* 45.

Nordin, U. & Lindholm, C-E. 1977 a. The vessels of the rabbit trachea and ischemia caused by cuff pressure. *Arch Oto-Rhino-Laryngol. 215,* 11.

Nordin, U., Engström, B. & Lindholm, C-E. 1977 b. Surface structure of the tracheal wall after different durations of intubation. *Acta Otolaryngol* (Stockh) *Suppl 345.*

Nordin, U., Källskog, Ö., Lindholm, C-E. & Wolgast, M. 1977 c. Transvascular fluid exchange in the tracheal mucosa. (Submitted to *Microvascular Res*)

Nordin, U., Lindholm, C-E. & Wolgast, M. 1977 d. Blood flow in the rabbit tracheal mucosa under normal conditions and under the influence of tracheal intubation. *Acta Anaesthesiol Scand.* (In press.)

Paegle, R.D. & Bernhard, W.N. 1975. Squamous metaplasia of tracheal epithelium associated with high-volume, low pressure airway cuffs. *Anesth Analg (Cleve) Vol. 54,* No 3, p. 340.

Pearson, F.G., Goldberg, M. & Da Silva, A.J. 1968. A prospective study of tracheal injury complicating tracheostomy with a cuffed tube. *Ann Otol Vol. 77,* No 5, Oct.

Rhodin, J.A.G. 1966. Ultrastructure and function of the human tracheal mucosa. *Am Rev Respir Dis Vol. 93,* No 3.

Safar, P., Berman, B., Diamond, E., Hoffman, K., Holtey, W., Moore, H. & Scoville, B. 1962. Cuffed tracheostomy tube versus tank respirator for prolonged artificial ventilation. *Arch Phys Med Rehabil 43,* 487.

Shelly, W.M., Dawson, R.D. & May, I.A. 1969. Cuffed tubes as a cause of tracheal stenosis. *J Thorac Cardiovasc Surg 57,* 623.

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Surface structure of the tracheal wall after different durations of intubation

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Abstract: The effect of a large tracheal tube cuff on the rabbit tracheal mucosa was investigated by phase contrast microscopy and scanning (SEM) and transmission (TEM) electron microscopy.

The effect of different durations of intubation on the extent of the damage was studied, the intubation time being varied between 1 and 4 hours.

The results were compared with those of a previous study in which the effect of different cuff-to-tracheal wall pressures (C-T pressures) on the extent of mucosal damage was investigated.

It was found that of these two factors, the C-T pressure has the greatest *relative* importance.

It is concluded that if the C-T pressure is kept low (below 20 mmHg), then the trachea is able to resist even a long duration of cuffed intubation, with use of a large, thin-walled cuff.

Introduction

Tracheal intubation over prolonged periods sometimes causes sufficient damage to the tracheal wall to result in a clinically significant tracheal stenosis. Incidences varying from 1.5 to 20 % have been reported (Pearson et al., 1968; Lindholm, 1969; Grillo, 1970). Geffin & Pontoppidan (1969) concluded that the stenosis most often was found in the region where the cuff had exerted its main pressure against the tracheal mucosa. The most widely used cuffs have been of the small-resting-diameter, small-resting-volume type, subsequently called *small* cuffs. Many publications have described the damage caused by this type of cuff and most authors have come to the conclusion that the main etiological factor in this damage is the high pressure exerted on the tracheal wall (Pearson et al., 1968; Cooper & Grillo, 1969; Shelly et al., 1969; Donnelly, 1969; Hedden et al., 1969; Grillo et al., 1971; Andrews & Pearson, 1971; Hilding, 1971; Magovern et al., 1972; Goldenberg & Pearson, 1972).

Further analyses of the cuff problem were made simultaneously by many research groups (Lomholt, 1967; Bryce et al., 1968; Carroll et al., 1969; Hedden et al., 1969; Cooper & Grillo, 1969; Geffin & Pontoppidan, 1969). The conclusion from these investigations was that the small cuff causes uncontrollable pressure against the tracheal wall and that it is impossible to measure the C-T pressure by recording the intracuff pressure.

The large-resting-diameter, large-residual-volume type of cuff (subsequently called the *large* cuff) was proposed by Lomholt (1967), Carroll et al. (1969), Cooper & Grillo (1969).

Geffin & Pontoppidan (1969) "prestretched" small plastic cuffs and thus converted them to large cuffs. All these groups found that the large cuff was able to "seal" at a much lower C-T pressure than the small cuff.

Several convincing reports have since demonstrated that cuff site tracheal injury is lower with large than with small cuffs (Cooper & Grillo, 1969; Grillo et al., 1971; Ching et al., 1971; Dunn et al., 1974; Mathias & Wedley, 1974; Paegle & Bernhard, 1975). This made us focus our interest on the *large* cuff in the present investigation and no comparative studies with small cuffs were included.

The aim of this investigation was to study tracheal damage caused by different durations of intubation, keeping the C-T pressure constant.

In another investigation (Nordin et al., 1977a) the tracheal damage caused by different C-T pressures was studied, keeping the duration of intubation constant.

Through these two investigations an attempt was made to answer the question of which is the most important factor in causing mucosal damage, the C-T pressure or the duration of intubation. Another aim was to create a model by which "standardized" tracheal damage of different degrees could be produced to allow a study of the regeneration of mucosa injured to a fairly well controlled depth. This study is in progress at present.

In parallel, we have studied

1) the vascular anatomy of the tracheal mucosa by arterial infusion of silicone rubber, and the effect of an inflated large cuff on the vascular bed (Nordin & Lindholm, 1977 b),

2) the capillary blood perfusion pressure and fluid balance of the tracheal mucosa, by the micropuncture technique (Nordin et al., 1977 c),

3) the effect of different C-T pressures on the capillary blood flow of the tracheal mucosa (Nordin et al., 1977 d).

Material and methods

Fifteen white rabbits, weighing between 2.0 and 3.4 kg, were used.

The structure of the tracheal wall was examined by direct observation—using a binocular preparation microscope (Wild M 5), and by phase contrast microscopy and scanning (SEM) and transmission (TEM) electron microscopy. The techniques for SEM and TEM were those currently used in our clinic (Ades & Engström, 1972). For SEM the specimens were fixed in buffered 2.5 % glutaraldehyde, dehydrated in 70 % ethanol and 70 % acetone and stored in pure acetone for at least two days before being dried by the critical point technique (Andersson, 1951). After being coated with gold in a sputtering system, the specimens were examined in a JSM-U 3 microscope.

For light microscopy and TEM two methods were used. With the first technique the specimens were fixed in buffered 2.5 % glutaraldehyde, post-fixed in 1.5 % osmium tetroxide for 1.5 h and embedded in Epon 812 (Luft, 1961). With the second technique the specimens used for SEM were immersed for 24 h in propylene oxide and embedded in Epon 812. The specimens for light microscopy and TEM were sectioned in an LKB Ultrotome. The TEM specimens were studied in a Siemens Elmiskop IA.

Intubation, tube and cuff. The rabbits were anesthetized by an intravenous injection of 2 % sodium pentobarbital (Nembutal®) in a dose of 50—60 mg/kg body weight. They breathed spontaneously throughout the experiment. A specially made PVC tube (Portex) with an inner diameter (ID) of 2.5 mm and an outer diameter (OD) of 3.5 mm was placed in the trachea by translaryngeal intubation. The cuff had been "prestretched" (Geffin & Pontoppidan, 1969) to obtain large-cuff properties (Lomholt, 1967; Carroll & Grenvik, 1973), in relation to the rabbit trachea. The thickness of the cuff wall varied slightly around 0.10 mm depending upon the degree of prestretching. When the cuff was deflated the diameter of the tube and cuff varied between 4.2 and 3.9 mm depending upon folds in the cuff. The length of the cuff was approximately 15 mm. The diameter of the trachea was about 5 mm.

The tube, with the cuff deflated, was placed in the cervical portion of the trachea, well below the larynx. The time of intubation was varied between 1 and 4 h. The results are presented in three different groups of C-T pressures, with variations of the intubation time within each group. The C-T pressure in the first group was fairly "normal", 20 mmHg, in the second group "medium", 50 mmHg, and in the third group "high", 100 mmHg. The pressures were measured according to Cox & Schatz (1974). By measuring the pressure in a cuff with large-cuff properties the C-T pressure is also known, being identical (Carroll et al., 1974). The animals were killed directly after the decided time of intubation by injection of Nembutal® and air.

Results

At a C-T pressure of 20 mmHg for *1 to 2 h* of intubation the mucosa on top of the cartilages was damaged to such an extent that it was partly denuded almost down to the basement membrane (Fig. 1 a). In this region about 50 % of the epithelial cells still remained, though they were damaged and somewhat compressed (Fig. 1 b, left).

In intercartilaginous regions most of the epithelium seemed well preserved, as seen at a low magnification (Fig. 1 a). At higher magnification it was obvious that some of these cells had lost their cilia, partly or completely (Fig. 1 c). TEM revealed that in some areas there was also incipient disintegration of the interior of the epithelial cells, with migration of leucocytes up to the basement membrane (Fig. 2 b).

At *3 h* of intubation the damage was more widespread (Fig. 3 a) and the epithelium was now partly compressed in the intercartilaginous areas also (Fig. 3 b). Areas approaching the top of the cartilages showed an increasing degree of damage, varying from partly denuded epithelium to a complete loss of epithelial cells and a denuded basement membrane (Fig. 3 c). In the figure some erythrocytes are visible.

At a C-T pressure of 50 mmHg for *2 h* of intubation most of the epithelial cells in the mucosa on top of the cartilages were destroyed or compressed. The basement membrane seemed intact but partly denuded (Fig. 4 a). The severely damaged areas on top of the cartilages were now wider compared with those at a C-T pressure of 20 mmHg. At *4 h* of intubation some parts of the mucosa in the intercartilaginous regions consisted of low epithelial cells covered by microvilli. These cells were intermingled with normally ciliated cells (Fig. 4 b).

At a C-T pressure of 100 mmHg for *1 h* of intubation the entire mucosa at cuff level was damaged to some extent. Small intercartilaginous areas of the mucosa were fairly well preserved, however, the cilia being only slightly compressed. On top of the cartilages, on the other hand, wide parts of the basement membrane were denuded and in some areas this was completely absent, leaving the mucosal stroma visible. At *2 h* of intubation intercartilaginous areas of the mucosa had lost their cilia and the epithelial cells were separated from each other. At *4 h* of intubation the mucosa covering the cartilages was sometimes destroyed down to the cartilage itself, and bacteria were found, for the first time, to be invading the damaged mucosa (Fig. 5).

Fig. 1. Scanning electron micrographs of rabbit tracheal mucosa exposed to a C-T pressure of 20 mmHg for 1—2 hours. *a.* At a low magnification (×80) it is seen that the mucosa on top of the cartilage is most severely damaged *(arrows). b.* The most severely damaged area overlying the cartilage (to the left) seen at a higher magnification (×800). In this region about 50% of the epithelial cells still remain. The intercartilaginous region (to the right) seems fairly well preserved, but a higher magnification (×1 700) in this area *(c)* shows that some of the cells have lost their cilia, partly or completely.

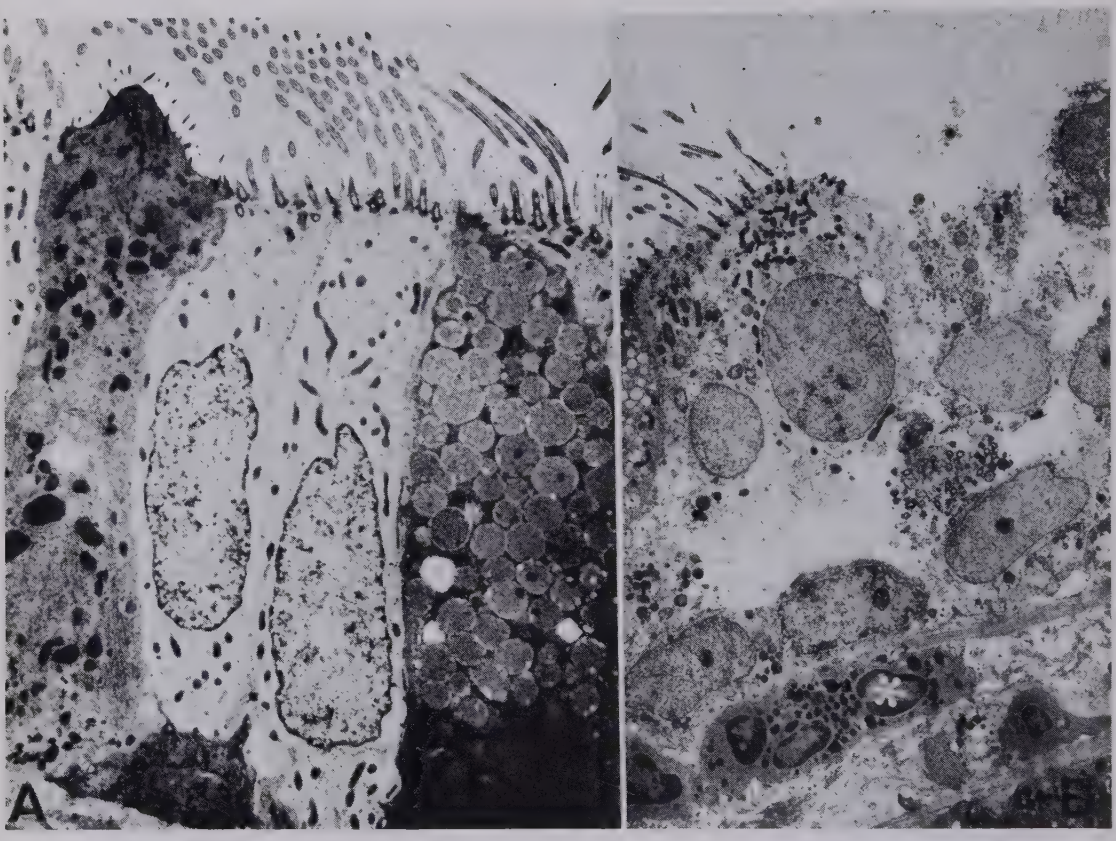

Fig. 2. Transmission electron micrographs from rabbit tracheal mucosa. *a.* Normal mucosa with ciliated cells and goblet cells. (×4 200). *b.* Mucosa exposed to a C-T pressure of 20 mmHg for 2 hours. In the most severely damaged area (to the right) most of the epithelial cells have sloughed off. At the borderline against the better preserved part of the mucosa (to the left in the photograph) there is incipient disintegration of the interior of the epithelial cells, with migration o leucocytes (*) up to the basement membrane. (×3 000).

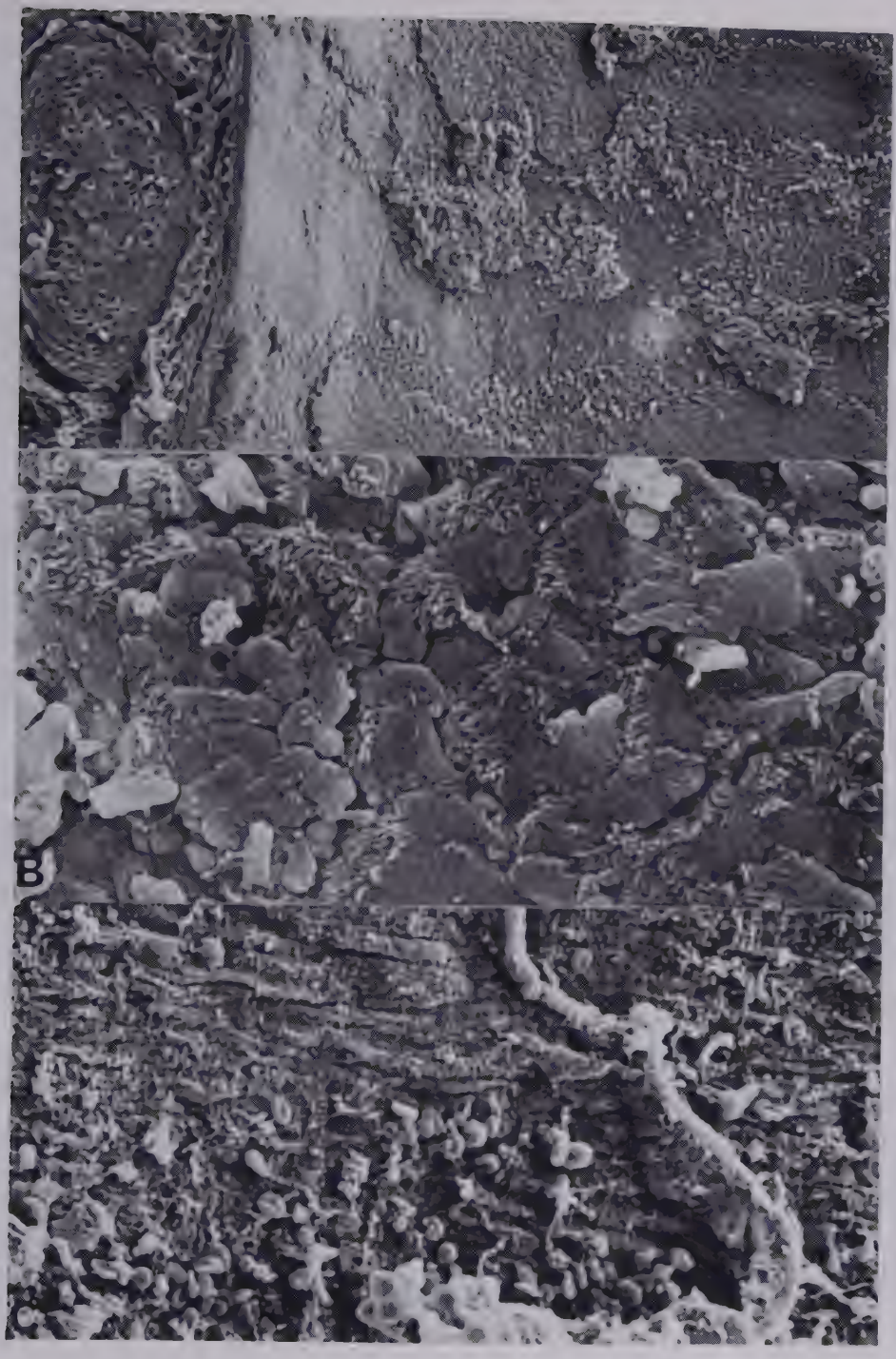

Fig. 3. Scanning electron micrographs of rabbit tracheal mucosa exposed to a C-T pressure of 20 mmHg for 3 hours. *a.* The damage here is more widespread than after 2 hours of intubation. The epithelium is now partly compressed in the intercartilaginous areas also *(b).* In more severely damaged areas only scattered epithelial cells remain and the basement membrane is partly denuded, *c.* *(a)* ×60. *(b)* ×900. *(c)* ×700.

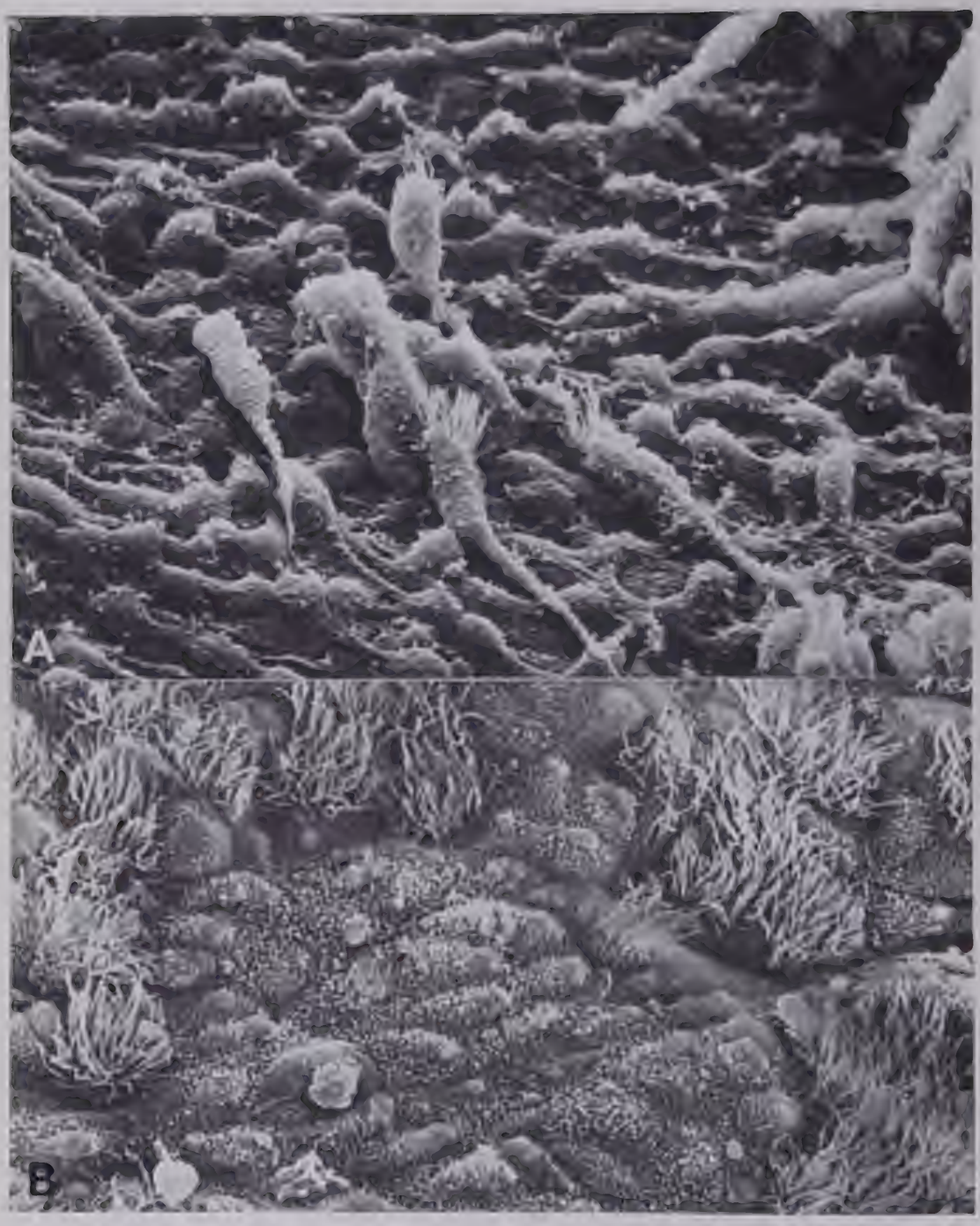

Fig. 4. Scanning electron micrographs of rabbit tracheal mucosa. *a.* Mucosa exposed to a C-T pressure of 50 mmHg for 2 hours. Most of the epithelial cells in the mucosa on top of the cartilages have been destroyed or compressed. The basement membrane seems to be intact. (×1 700). *b.* Intercartilaginous region of a mucosa exposed to 50 mmHg for 4 hours. Among normally ciliated epithelial cells, low epithelial cells covered by microvilli are seen. Whether this is a sign of incipient disintegration of the cilia or a sign of incipient cilial regeneration cannot be decided. (×3 000).

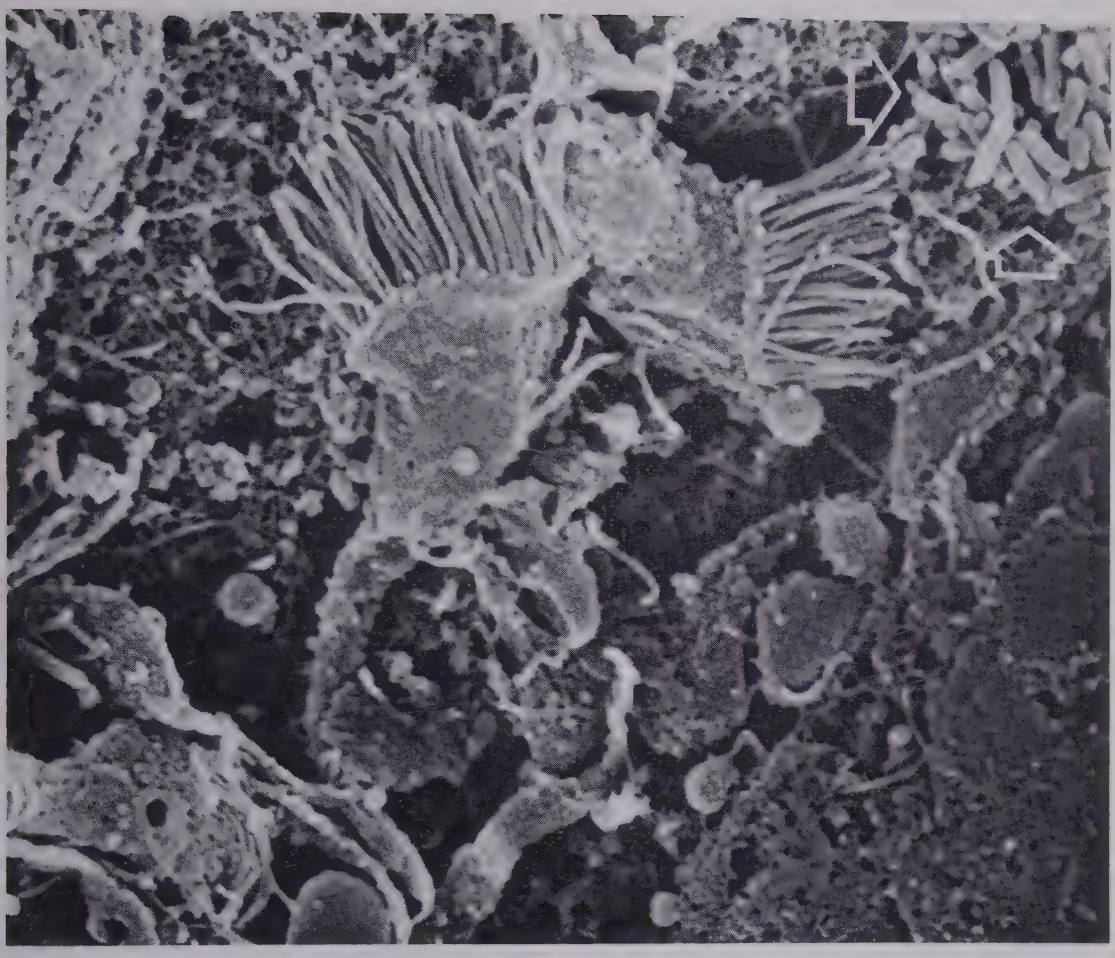

Fig. 5. Scanning electron micrograph of rabbit tracheal mucosa exposed to a C-T pressure of 100 mmHg for 4 hours. The exposed mucosal stroma is—the only time in all our experiments—invaded with bacteria *(arrows)*. (×4 000).

Discussion

A C-T pressure of 20 mmHg for *up to 2 h* of intubation did not cause significantly more damage than was found after 15 min of intubation at the same pressure, in another investigation (Nordin et al., 1977 a). In intercartilaginous regions in the present study some epithelial cells were still preserved, but the mucosa seemed more "swollen" (Fig. 1 a) than after 15 min of intubation.

A C-T pressure of 50 mmHg for *up to 2 h* of intubation did not seem to cause significantly greater damage than when this pressure was applied during 15 min of intubation. The basement membrane seemed intact but partly denuded (Fig. 4 a). At *4 h* of intubation some parts of the mucosa in the intercartilaginous regions consisted of low epithelial cells covered by microvilli. These cells were intermingled with normally ciliated cells. Whether this was an expression of incipient disintegration of the cilia or a sign of incipient cilial regeneration, only 4 h after the damage was produced, cannot be answered at present. This question is being examined further in an investigation now in progress (Nordin), where the regeneration of cuff-induced mucosal damage is being studied.

C-T pressure of 100 mmHg. At this pressure it seemed in the previous investigation (Nordin et al., 1977 a) as if the basement membrane had begun to disintegrate after only 15 min of intubation. In the present study it was seen that after *1 h* of intubation the damage was more serious, with areas in which the basement membrane was completely absent, leaving the mucosal stroma exposed. At *4 h* of intubation the damage sometimes penetrated almost down to the cartilage, and considerable bacterial invasion of damaged mucosa was found. This was the only time in all our experiments at which bacteria were observed. It thus seems that even with fairly penetrating damage, local infection does not begin to play a serious role until after about four hours of intubation. There is little reason to believe that the bacteria arrived there by contamination, as this *never* happened with less severely damaged animals.

In our opinion the C-T pressure is more important than the duration of intubation for the occurrence of tracheal damage. This is certainly true for "ordinary" periods of intubation, i.e. up to three hours. This finding is in accordance with the observations reported by Mathias & Wedley (1974).

Conclusions

1. Tracheal cuff damage is highly influenced by the product of C-T pressure and duration of intubation.

2. Of these factors, C-T pressure has the greatest importance.

3. This means that if the C-T pressure is kept low, then the trachea is able to resist even a long duration of cuffed intubation.

4. In addition to the above-mentioned traumatizing factors, other factors are also of importance. These include the shape of the tube and cuff, physical and chemical properties of the tube and cuff material, local infection, and the general condition of the patient.

5. To diminish tracheal lesions, the product of all traumatizing factors should be kept as low as possible. The anesthetist should pay special attention to the following:

I. A high quality tube which will easily adapt to the anatomy of the airway should be chosen, and should be equipped with a thin-walled large cuff.

II. Recordings should be made to ensure a C-T pressure below 20 mmHg.

III. Movements of the cuff relative to the tracheal wall should be minimized.

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Zusammenfassung

Die Wirkung einer grossen trachealen Schlauchmanschette auf die Schleimhaut der Kaninchentrachea wurde sowohl mit Fasenkontrastmikroskopie als auch Scanning- (SEM) und Transmissionselektronenmikroskopie (TEM) untersucht.

Der Einfluss verschieden langer Intubationsdauer auf das Ausmass der Schädigung wurde studiert, wobei die Intubationsdauer zwischen ein bis vier Stunden wechselte.

Die Ergebnisse wurden mit denen einer früheren Untersuchung verglichen, in welcher der Einfluss verschiedener "cuff-to-tracheal" Wanddrucke (C-T-pressures) auf die Ausdehnung des Schleimhautschadens ermittelt wurde.

Es zeigte sich, dass von diesen beiden Faktoren der C-T Druck die grössere relative Bedeutung hat.

Daraus lässt sich schliessen, dass bei Niedrighalten des C-T Druckes unter 20 mm Hg) die Trachea auch einer länger währenden Intubation standhalten kann, wenn eine grosse, dünnwandige Schlauchmanschette angewandt wird.

References

Ades, H.W. & Engström, H. 1972. Inner ear studies. *Acta Otolaryngol* (Stockh) *Suppl 301.*

Andersson, T.F. 1951. Technique for the preservation of three-dimensional structure in preparing specimens for the electron microscope. *Trans NY Acad Sci 13,* 130.

Andrews, M.J. & Pearson, F.G. 1971. Incidence and pathogenesis of tracheal injury following cuffed tube tracheostomy with assisted ventilation: analysis of two year prospective study. *Ann Surg 173,* 249.

Bryce, D.P., Briant, T.D.R. & Pearson, F.G. 1968. Laryngeal and tracheal complications of intubation. *Ann Otol 77,* 442.

Carroll, R.G. & Grenvik, Å. 1973. Proper use of large diameter, large residual volume cuffs. *Crit Care Med 1,* 153.

Carroll, R.G., Hedden, M. & Safar, P. 1969. Intratracheal cuffs: performance characteristics. *Anesthesiology, Vol. 31,* No 3.

Carroll, R.G., McGinnis, G.E. & Grenvik, Å. 1974. Performance characteristics of tracheal cuffs. *Int Anesthesiol Clin, Vol. 12,* No 3, p. 111.

Ching, N.P., Ayres, S.M., Paegle, R.P., Linden, J.M. & Nealon, T.F. 1971. The contribution of cuff volume and pressure in tracheostomy tube damage. *J Thorac Cardiovasc Surg 62,* 402.

Cooper, J.D. & Grillo, H.C. 1969. Experimental production and prevention of injury due to cuffed tracheal tubes. *Surg Gynec Obstet 129,* 1235.

Cooper, J.D. & Grillo H.C. 1969. The evolution of tracheal injury due to ventilatory assistance through cuffed tubes. *Ann Surg 169,* 334.

Cox, P. & Schatz, E. 1974. Pressure measurements in endotracheal cuffs: a common error. *Chest 65,* 84.

Donnelly, W.H. 1968. Histopathology of endotracheal intubation. *Arch Path 88,* 511.

Dunn, R.C., Dunn, D.L. & Moser, K.M. 1974. Determinants of tracheal injury by cuffed tracheostomy tubes. *Chest 65,* 128.

Geffin, B. & Pontoppidan, H. 1969. Reduction of tracheal damage by prestretching of inflatable cuffs. *Anesthesiology 31,* 462.

Goldenberg, M. & Pearson, F.G. 1972. Patnogenesis of tracheal stenosis following

tracheostomy with a cuffed tube. *Thorax 27,* 678.

Grillo, H.C. 1970. Surgery of the trachea. *Current problems in surgery, p. 3,* Year book medical publishers, Inc., Chicago.

Grillo, H.C., Cooper, J.D., Geffin, B. & Pontoppidan, H. 1971. A low pressure cuff for tracheostomy tubes to minimize tracheal injury—a comparative clinical trial. *J Thorac Cardiovasc Surg 62,* 898.

Hedden, M., Ersoz, C.J. & Safar, P. 1969. Tracheoesophageal fistulas following prolonged artificial ventilation via cuffed tracheostomy tubes. *Anesthesiology 31,* 282.

Hilding, A.C. 1971. Laryngotracheal damage during intratracheal anaesthesia. *Ann Otol 80,* 565.

Lindholm, C-E. 1969. Prolonged endotracheal intubation. *Acta Anaesthesiol Scand Suppl XXXIII.*

Lomholt, N. 1967. A new tracheostomy tube: Cuff with controlled pressure on the tracheal mucous membrane. *Acta Anaesthesiol Scand 11,* 311.

Luft, J.H. 1961. Improvements in epoxy resin embedding methods. *J. Biophys Biochem Cytol. 9,* 409.

Magovern, G.J., Shively, J.G., Fecht, D. & Thevoz, F. 1972. The clinical and experimental evaluation of a controlled-pressure intratracheal cuff. *J Thorac Cardiovasc Surg 64,* 747.

Mathias, D.B. & Wedley, J.R. 1974. The effects of cuffed endotracheal tubes on the tracheal wall. *Br J Anaesth 46,* 849.

Nordin, U., Engström, B., Jansson, B. & Lindholm, C-E. 1977 a. Surface structure and vascular anatomy of the tracheal wall under normal conditions and after intubation. *Acta Otolaryngol* (Stockh) *Suppl 345.*

Nordin, U. & Lindholm, C-E. 1977 b. The vessels of the rabbit trachea and ishemia caused by cuff pressure. *Arch Oto-Rhino-Laryngol. 215,* 11.

Nordin, U., Källskog, Ö., Lindholm, C-E. & Wolgast, M. 1977 c. Transvascular fluid exchange in the tracheal mucosa. (Submitted to *Microvascular Res*)

Nordin, U., Lindholm, C-E. & Wolgast, M. 1977 d. Blood flow in the rabbit tracheal mucosa under normal conditions and under the influence of tracheal intubation. *Acta Anaesthesiol Scand.* (In press.)

Paegle, R.D. & Bernhard, W.N. 1975. Squamous metaplasia of tracheal epithelium associated with high-volume, low pressure airway cuffs. *Anesth Analg (Cleve) Vol. 54,* No 3, p. 340.

Pearson, F.G., Goldberg, M. & Da Silva, A.J. 1968. A prospective study of tracheal injury complicating tracheostomy with a cuffed tube. *Ann Otol Vol. 77,* No 5, Oct.

Shelly, W.M., Dawson, R.D. & May, I.A. 1969. Cuffed tubes as a cause of tracheal stenosis. *J Thorac Cardiovasc Surg 57,* 623.

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